THIOPYRAN ROUTE TO POLYPROPIONATES: SIMULTANEOUS TWO DIRECTIONAL AND ENANTIOTOPIC GROUP SELECTIVE ALDOL REACTIONS.

A Thesis Submitted to the
College of Graduate Studies and Research
in Partial Fulfillment of the Requirements
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By
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Abstract

The sequential aldol reactions of thiopyran derivatives **112** and **119** to rapidly generate hexapropionate building blocks in two carbon-carbon forming steps has been well studied within the Ward group. An extension of this strategy to generate non-racemic tetra- and hexapropionate fragments involved the use of non-racemic **119** which was obtained via resolution of the acid derivate **131**.

Part of the present work concerns the preparation of non-racemic **119** via enantioselective protonation of various thiopyran based ester derivatives. The trend observed in the ee obtained for the various ester derivatives is consistent with what has been previously observed by other groups.

Section 2.3 discusses the use of β-ketocarbonyl analogues of thiopyranone in vinylogous aldol reactions. A β-ketocarbonyl analogue was prepared and shown to undergo stereoselective aldol reactions under previously established condtions. The stereoselectivities of the reactions were in all cases consistent with what has been previously observed for the aldol reactions of **112** and **119** within the group.

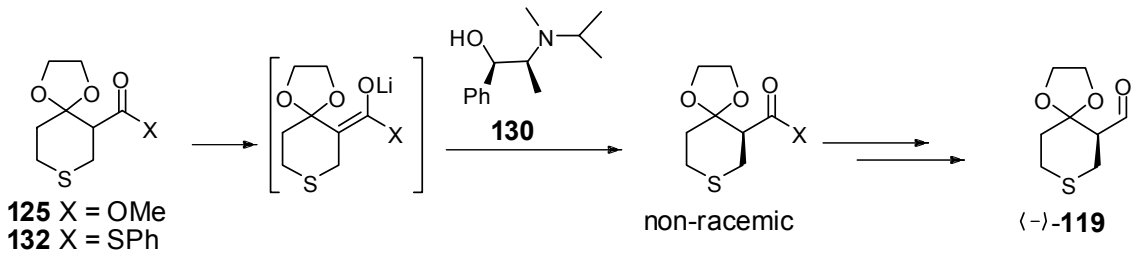
Section 2.4 discusses the preparation of a *meso* dialdehyde derivative of thiopyranone (**196**) and it's use in a simultaneouse two directional aldol reaction to generate a hexapropionate building block with six stereocenters in a one pot reaction. The *meso* adduct **202as** generated was successfully desymmetrized via enantioselective enolization to afford an enantioenriched adduct with seven stereogenic centers.

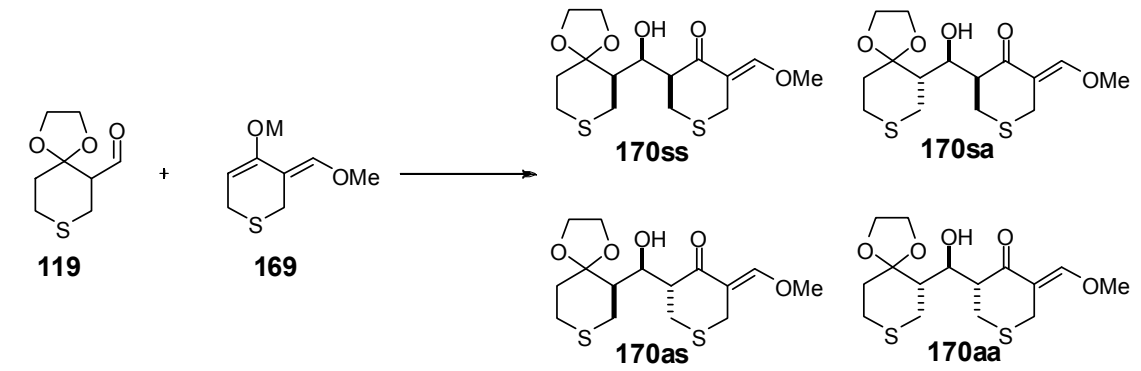
The *meso* dialdehyde **196** was also desymmetrized via an enantiotopic group selective aldol reaction promoted with (*S*)-proline. This reaction proceeds via a dynamic kinetic and thermodynamic resolution to afford a single stereoisomer. The enantioenriched aldol adduct was converted to a tetrapropionate unit and also demonstrated after derivatization to undergo a

second aldol reaction affording a non-racemic hexapropionate synthon. This chemistry is discussed in section 2.5.

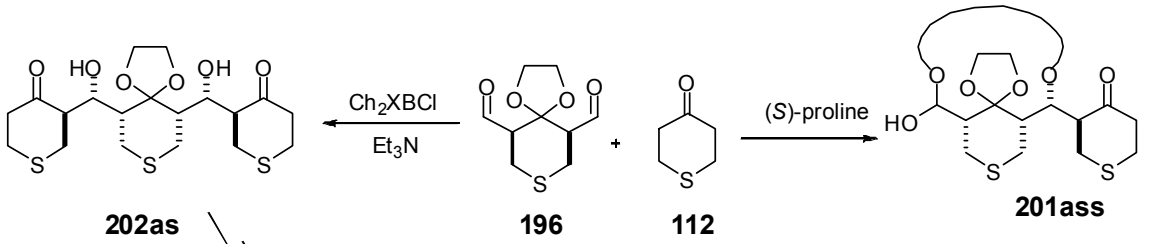
Section 2.6 discuses the assignment of the relative and absolute configurations of the various aldol adducts via NMR and X-ray.

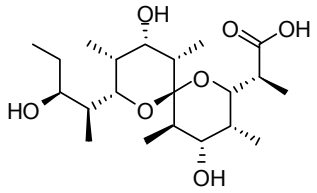
To demonstrate the synthetic usefulness of this research, the hexapropionate synthon **202as** was used as a template towards the confirmation or reassignment of the core spiroketal structure reported for enteridic acid.





all four diastereoisomers prepared selectively





enteridic acid

Acknowledgments

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I would like to thank my Family for all the moral and spiritual support they gave over the years. Thanks for everything!.

Dedication

To the memory of a wise woman who once told me;

"Never sell or exchange your dreams no matter the price"

Madam M.A. Akinnusi 19/08/1943-17/07/2004

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List of abbreviations

Ac	acetyl (ethanoyl)
Ac_2O	acetic anhydride
AcCl	acetyl chloride
AcOH	acetic acid
aq	aqueous
ap or app	apparent (NMR)
9-BBN	9-borobicyclo[3.3.1]nonane
BHT	2,6-di-*tert*-butyl-4-methylphenol
Bn	benzyl
Boc	*t*-butoxycarbonyl
Bu	butyl
Bz	benzoyl
^{13}C NMR	carbon-13 nuclear magnetic resonance
Chx	cyclohexyl
CI	chemical ionization
CSA	camphorsulfonic acid
DCC	1,3-dicyclohexylcarbodiimide
DET	diethyl tartrate
DIBAL	diisobutylaluminium hydride
dil.	dilute
DIPEA or DIEA	diisopropylethylamine
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMF	dimethylformamide
DMP	2,2-dimethoxypropane

DMS	dimethylsulphide
DMSO	dimethyl sulphoxide
dr	diastereomers ratio
DRIFT	diffuse reflectance Fourier transform infrared
ee	enantiomeric excess; for a mixture of two enantiomers *R* and *S*, ee=|([*R*]-[*S*])|/([*R*]+[*S*]) x 100%
EI	electron impact ionization
equiv	equivalent(s)
er	enantiomeric ratio; ratio of (*R*) to (*S*) (or *S* to *R*)
Et	ethyl
Et_2O	diethyl ether
Et_3N	triethylamine
EtOAc	ethyl acetate
$Eu(fod)_3$	tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato) europium (III)
FAB	fast-atom bombardment
FCC	flash column chromatography
FID	free induction decay (in NMR spectroscopy)
fod	6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato
FTIR	Fourier transform infra red
^{1}H NMR	proton nuclear magnetic resonance
h	hour(s)
H-bonding	hydrogen bonding
HMBC	heteronuclear multiple bond correlation (2 and 3 bond J_{CH} correlation with inverse detection)

HMQC	heteronuclear multiple quantum coherence (1 bond J_{CH} correlation with inverse detection)
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
i-Bu	isobutyl (2-methylpropyl)
IMDA	intramolecular Diels-Alder
i-Pr	isopropyl
IR	infrared
LA	Lewis acid
LB	Lewis base
LDA	lithium diisopropylamide
LRMS	low resolution mass spectroscopy
MAC	methyl acrylate
m-CPBA	3-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
MeLi	methyllithium
MeOH	methanol
MHz	megahertz; 10^6 Hertz
min	minute(s)
MOM	methoxymethyl
MPC	medium pressure chromatography
p-MPM or *p*-PMB	*p*-methoxybenzyl or *p*-methoxyphenylmethyl
MS	mass spectrometry

MS4A	molecular sieves 4Å
MsCl	methanesulphonyl chloride
MTPA	2-methoxy-2-(trifluoromethyl)-2-phenylacetic acid
MTPACl	2-methoxy-2-(trifluoromethyl)-2-phenylacetyl chloride
MVK	methyl vinyl ketone
na	not applicable
NBS	N-bromosuccinimide
n-BuLi	*n*-butyllithium
nd	not determined
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser enhancement
NR	no reaction
OTBDMS	*tert*-butyldimethylsilyloxy
OTf	trifluoromethanesulfonyloxy (CF_3SO_2O)
Ph	phenyl
PMB or MPM	*p*-methoxybenzyl or *p*-methoxyphenylmethyl
^{i}Pr	isopropyl
PTLC	preparative thin layer chromatography
p-TsOH	*p*-toluenesulfonic acid (4-methylbenzenesulfonic acid)
pv	pivaloyl
Pyr	pyridine
rt	room temperature; ca. 22-24 ˚C
sat.	saturated; as in a saturated aqueous solution
s	second(s)
TADDOL	(2*R*,3*R*)-2,3-O-(1-phenylethylidene)-1,1,4,4-tetraphenyl-1,2,3,4-butanetetrol

TBAF	tetrabutylammonium fluoride
TBDMS or TBS	*t*-butyldimethylsilyl
TBDMSCl or TBSCl	*t*-butyldimethylsilyl chloride
TBDMSCN	*t*-butyldimethylsilyl cyanide
TBDPS	*t*-butyldiphenylsilyl
TBDPSCN	*t*-butyldiphenylsilyl cyanide
TBS or TBDMS	*t*-butyldimethylsilyl
t-Bu	*tert*-butyl (1,1-dimethylethyl)
t-BuLi	*tert*-butyllithium
TEA	triethylamine
TES	triethylsilyl
TESCN	triethylsilyl cyanide
TESOTf	triethylsilyl triflate
Tf	trifluromethanesulphonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran (oxolane)
TIPS	triisopropylsilyl
TIPSOTf	triisopropylsilyl trifluoromethanesulfonate
TLC	thin-layer chromatography
TMS	trimethylsilyl or tetramethylsilane
TMSCl	trimethylsilyl chloride(chlorotrimethylsilane)
TMSCN	trimethylsilyl cyanide(cyanotrimethylsilane)
TMSOTf	trimethylsilyl trifluoromethanesulfonate
Tol	toluene
Tr	triphenylmethyl (trityl)

TS	transition state
TsCl	4-methylbenzenesulfonyl chloride (toluenesulphonyl chloride)
v/v	volume relative to volume measure
$VO(acac)_2$	vanadyl acetylacetonate
w/v	weight relative to volume measure

Chapter 1

Introduction

1.1 Polypropionates

Polypropionates are a class of naturally occurring compounds derived from the polyketide biosynthetic pathway. A basic structural marker for this group of compounds is the consecutive stereogenic centers substituted with alternating methyl and oxygen groups (hydroxyl or oxo groups) (Figure 1).

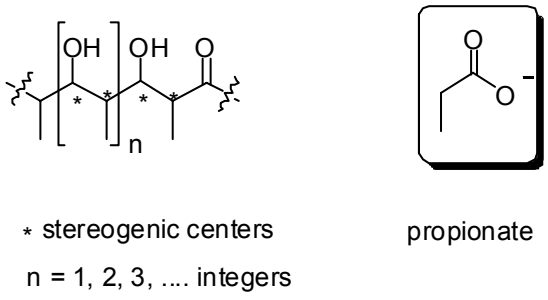


Figure 1: Polypropionate fragment.

The biological activities exhibited by many natural products containing polypropionate fragments, such as antibiotic, antitumour, antiparasitic, immunomodulation and toxic properties, have prompted a great deal of research on their isolation, characterization, and total synthesis.[1-3] Examples of the synthesis and isolation of members from this class of compounds with

interesting biological activity includes; erythromycin A (**1**),[4-6], rifamycin S (**2**),[7,8] enteridinine A (**3**),[9] and siphonarin B (**4**),[10] (Figure 2).

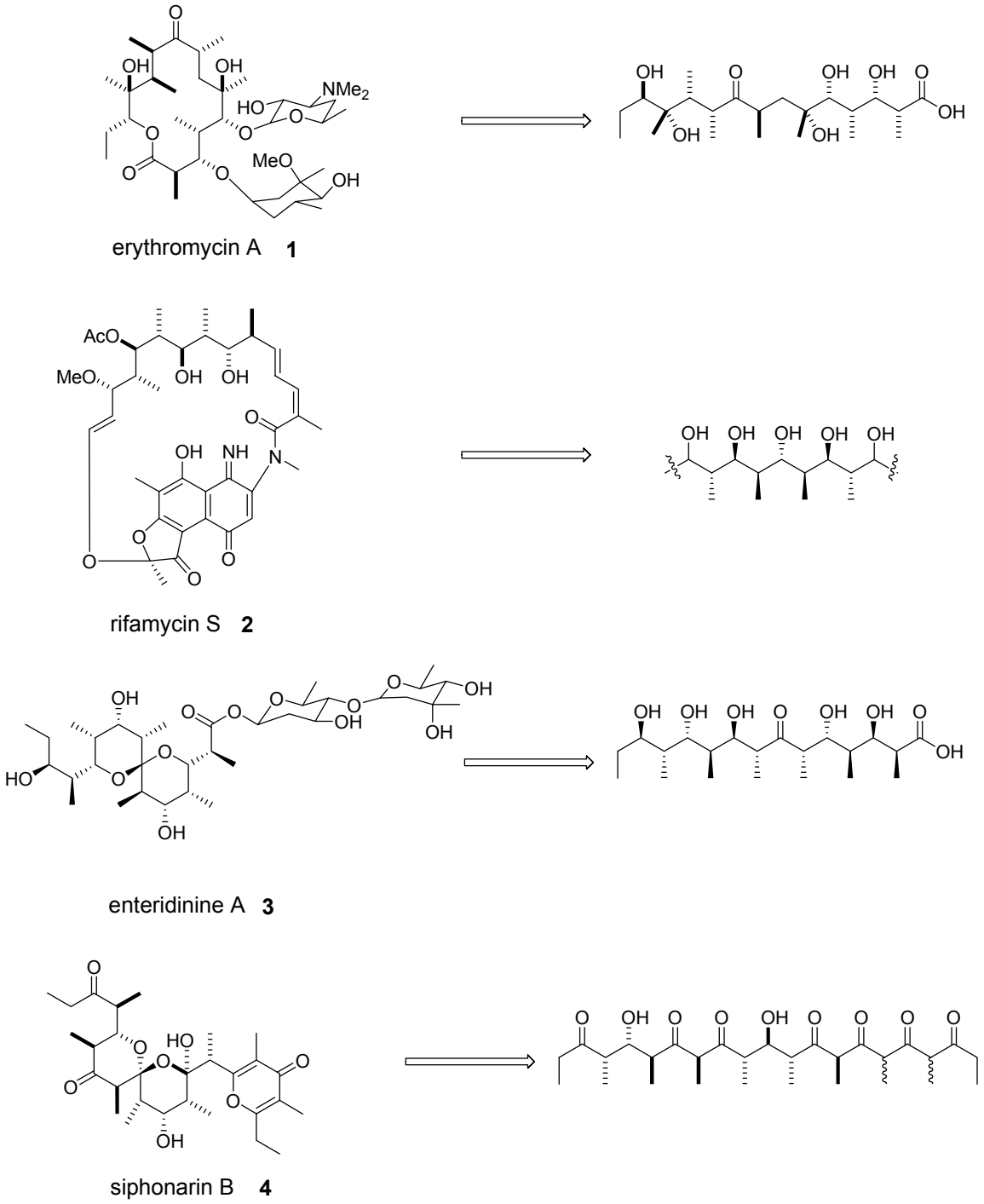


Figure 2: Examples of polypropionate natural products

Apart from the wide range of biological activities this class of compounds exhibits, their structural complexity makes them equally attractive targets. Over the years, a number of very efficient methods for the synthesis of polypropionate fragments of natural products have been developed among which are aldol reactions,[2,11-33] Diels-Alder reaction,[34-37] Claisen rearrangement,[38-40] allenylmetal addition reaction,[41-46] crotyl metal addition,[47-51] metal catalysed reduction,[52] cyclo addition reaction,[53,54] addition to dianions[55] and iodocarbonylation.[56] The aldol reaction in particular has received a lot of attention as is evident in the number of total syntheses achieved using this method[2] in one or more key steps. Numerous stereoselective aldol reactions have been developed. In most cases, the stereoselectivity of an aldol reaction is effected by chiral auxiliaries attached to the enolate (the nucelophilic unit),[57-59] or by chiral catalysts,[60,61] or chiral reagents[10,19,26,62] or by using enantioenriched starting materials.[7] The aldehyde units (the electrophilic unit) used in aldol reactions are often chiral and are usually obtained in enantioenriched form prior to use.

The use of *meso* compounds in stereoselective synthesis of natural products has attracted a lot of attention within the last 20 years.[63] Of particular interest are *meso* bifunctional compounds in which stereoselective reactions with one of the functional groups readily furnishes a chiral enantioenriched material.[63-66] *Meso* dialdehydes are a subset of bifunctional compounds that have been used in a number of reactions to generate enantiopure fragments of naturally occurring compounds.[63] The use of these types of compounds to generate enantiopure fragments via enantiotopic group selection and simultaneous chain extension followed by differentiation of the terminal groups is discussed in detail in the following sections.

1.2 *Meso* bifunctional compounds.

1.2.1 Introduction

The use of *meso* bifunctional compounds in the syntheses of natural products has been well documented.[63] *Meso* bifunctional compounds such as anhydrides,[67] dialdehydes,[8,46,68-70] bisepoxides[71] and diols[72-74] to name a few have found applications in the total synthesis of compounds such as rifamycin S,[7,8] denticulatins,[38,75] and mycoticin A.[76] There are two basic approaches commonly employed in utilizing these types of compounds, the first of which is a sequential linear approach that involves enantiotopic group selective reactions and the second is a simultaneous two directional chain elongation[66] followed by differentiation of the terminal ends. The focus of this section of my thesis will be on the use of *meso* dialdehydes in studies directed towards the synthesis of natural products using various reaction types under these two approaches.

1.2.2 Enantiotopic group selective desymmetrization of *meso* dialdehydes.

The enantiotopic groups in various dialdehydes* have been successfully differentiated using various reaction types. Figure 3 gives an overview of examples of the different types of *meso* dialdehydes that have been employed in the synthesis of natural products.

* Dialdehydes of C_S and C_I symmetry will have enantiotopic groups. Such dialdehydes are *meso* if they contain 2 or more (chirotopic) streogenic elements.

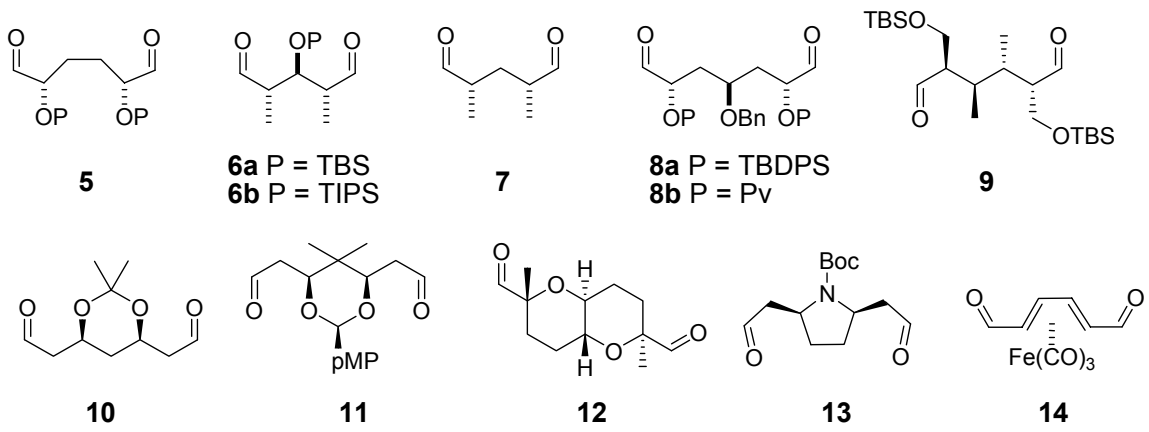


Figure 3: Examples of *meso* dialdehydes used in total synthesis.

Meso dialdehydes have four different faces that can react with a nucleophile. Attack on any of the four faces generally leads to a different stereoisomer and as such the use of these types of compound in asymmetric synthesis is not trivial (Figure 4).

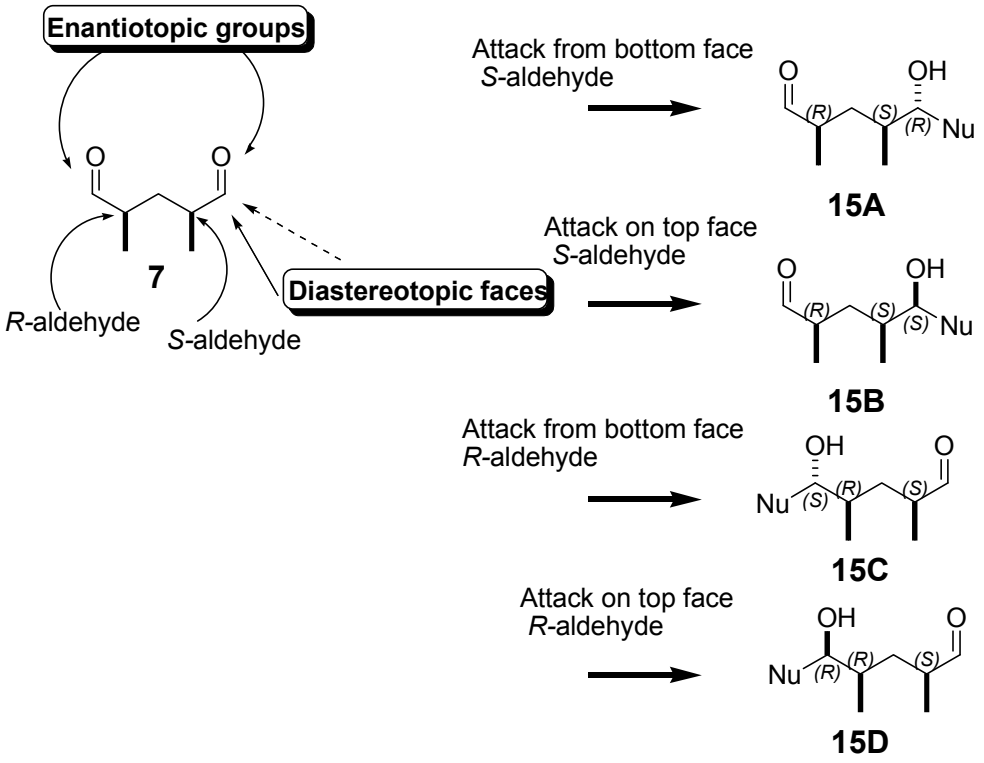
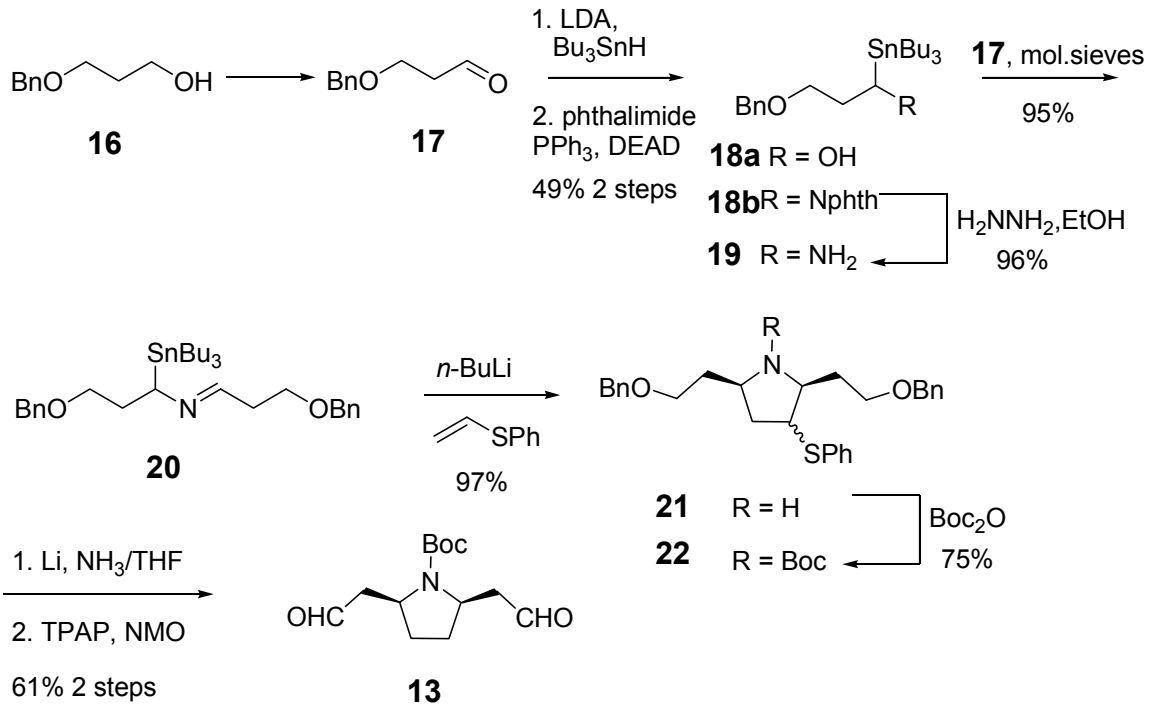


Figure 4: Addition to the enantiotopic and diastereotopic faces of a *meso* dialdehyde

For these types of compounds to be of any synthetic use, all four faces of the aldehyde groups must be well differentiated during a reaction. To achieve this, various chiral mediators have been employed either as a chiral auxiliary attached to the nucleophile [75,77] or as a catalyst [78] to help discriminate the faces.

A major limitation associated with the use of meso bifunctional compounds in asymmetric synthesis is the fact that these types of compounds are generally not readily available. They are often obtained via lengthy and/or complex synthetic processes. For example, in Pearson and Mans'[78] synthesis of the un-natural (+)-Cocaine, the meso dialdehyde **13** was obtained in ca 20% yield over 9 steps from commercially available materials (Scheme 1).



Scheme 1: Pearson and Mans synthesis of a *meso* dialdehyde.

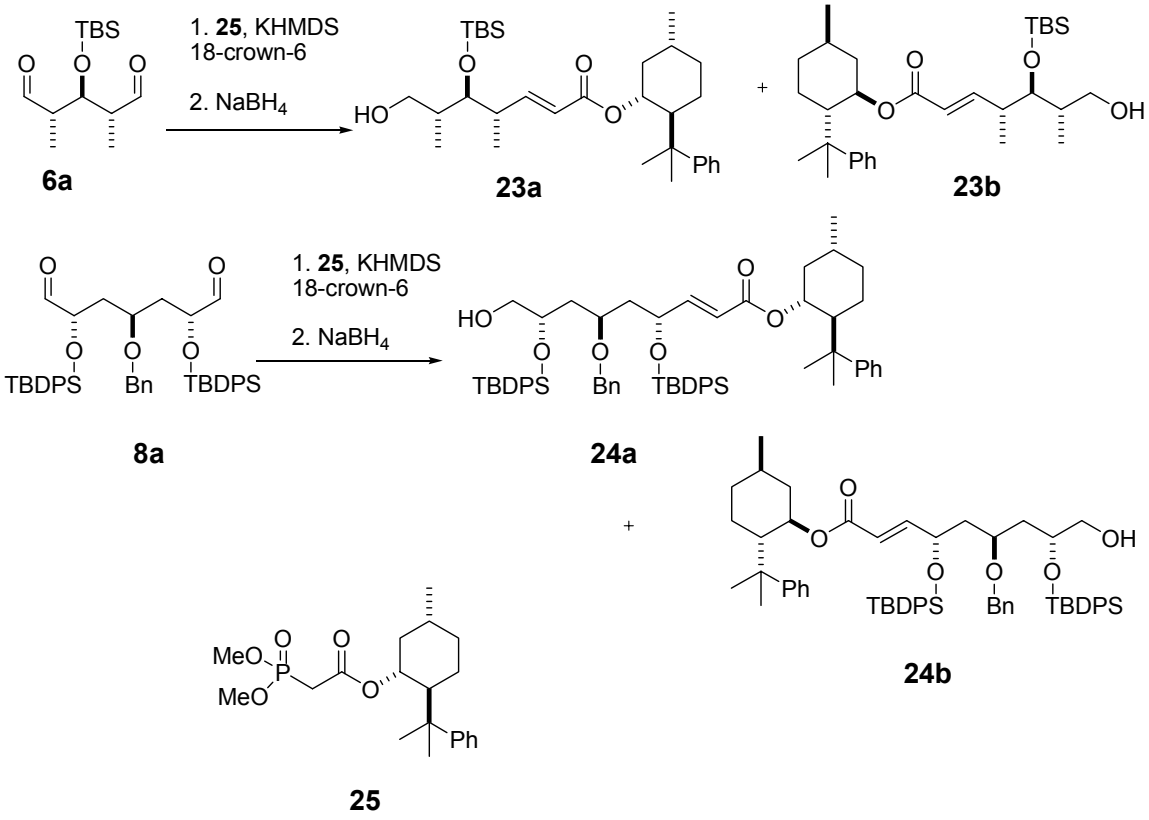
A number of reactions such as Horner-Wadsworth-Emmons,[69] aldol, [75] crotylation,[79,80] allylation[46,81] and alkylation[70,82] have been employed to differentiate the enantiotopic groups in *meso* dialdehydes. The development and scope of these reactions for total synthesis of natural products are discussed in the following sections.

1.2.2.1 Enantiotopic group selection via asymmetric Horner-Wadsworth-Emmons reaction.

Rein and Kann[69] gave the first example of the use of *meso* dialdehyde in a non-enzymatic enantiotopic group selective reaction (EGS) via an asymmetric Horner-Wadsworth-Emmons reaction.[83-85] A phosphonate derived from menthol

(Scheme 2) was employed as the chiral reagent in their investigation of the desymmetrization of meso dialdehydes **5**, **6** and **8**.

Employing an excess of the dialdehyde to suppress the formation of the double addition product, the reactions of **25** with **6a** and **8a** gave similar results in terms of diastereoselectivity (Table 1) indicating that the type of atom α– to the aldehyde group had little influence on the outcome of the addition. The reaction temperature influenced both the yield and the diastereoselectivity of the addition (from 6:1 at -78 ^{o}C to 10:1 at -100 ^{o}C; Table 1 entry 1 and 2). Surprisingly, the geometry of the olefin formed from the reaction was determined to be *E* in spite of the reaction conditions that are generally known to favor the formation of *Z* diastereomer.[86] To rationalize and understand the reason for this observation, computational studies were carried out using high level quantum methods.[87]



Scheme 2: Desymmetrization of *meso* dialdehydes **6a** and **8a** via asymmetric HWE reaction

Table 1 Reactions of Phosphonate **25** with dialdehyde **6a** and **8a**.

entry	Substrate (equiv)	temp (^{o}C)	reaction time(h)	ratio **23a:23b**	ratio **24a:24b**	yield (%)
1	**6a**(2.0)	-78	2.5	87:13	-	88
2	**6a**(2.1)	-100	5	90:10	-	87
3	**6a**(1.3)	-100	5	91:9	-	77
4	**6a**(1.2)	-78	3.5	97:3	-	36
5	**6a**(1.1)	-100	8	95:5	-	53
6	**8a**(2.0)	-78	4	-	87:13	68
7	**8a**(2.0)	-100	15	-	89:11	50
8	**8a**(1.2)	-100	15	-	92:8	49
9	**8a**(1.2)	-78	6.5	-	89:11	60

In their study, two transition states were identified to be significant for the determination of the product selectivity (Figure 5). The first is the transition state involved in the addition of the phosphonate enolate to the aldehyde and the second the transition state leading to the formation of the oxephosphetane intermediate. In both cases, product formation would be influenced by 3 factors: (i) the configuration at the α-stereocenter in the aldehyde, as this would dictate the face of the aldehyde most favored to be attacked, (ii) the chiral auxiliary on the phosphonate, this would dictate the face of the phosphonate enolate that does the attack, and (iii) the alkoxy group in the phosphonate ester, this would influence both the aldehyde and enolate face selectivity.

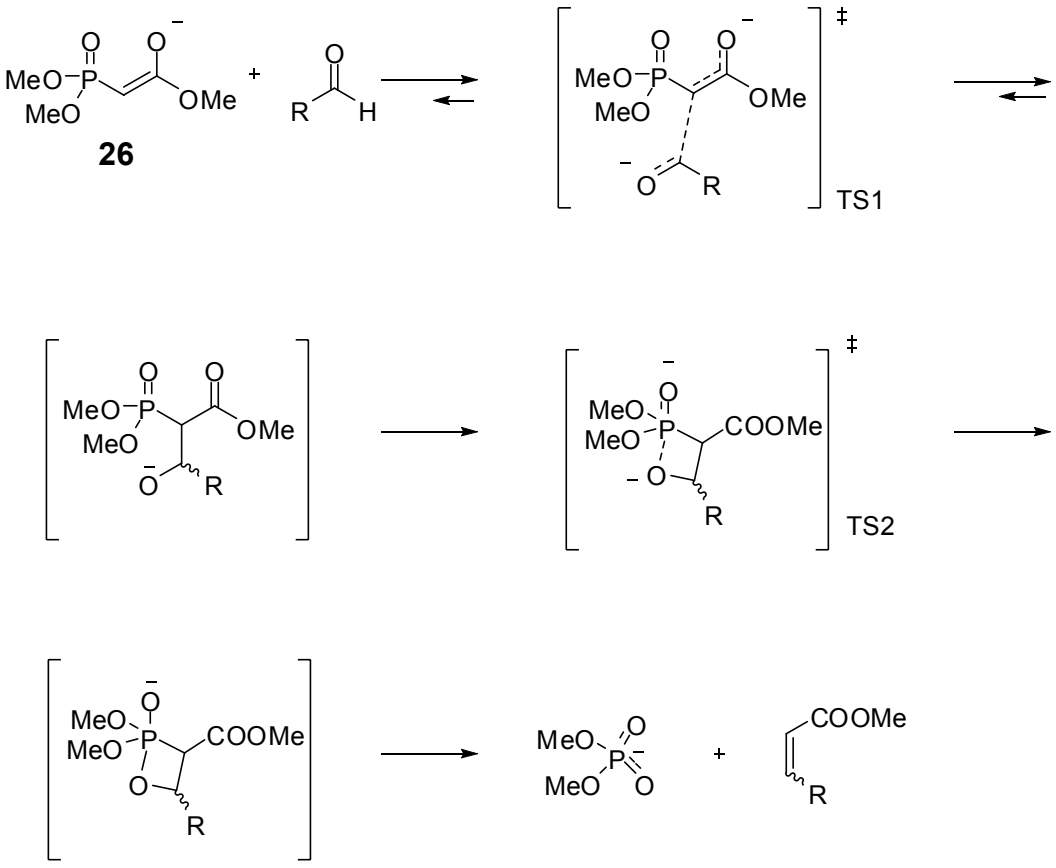


Figure 5: Transition state model to explain the HWE reaction of **26** a phosphonate enolate with an aldehyde.

A study to test the conclusions of the computational study was carried out using different analogues of the phosphonate [88] and a more synthetically useful *meso* dialdehyde (Figure 6).

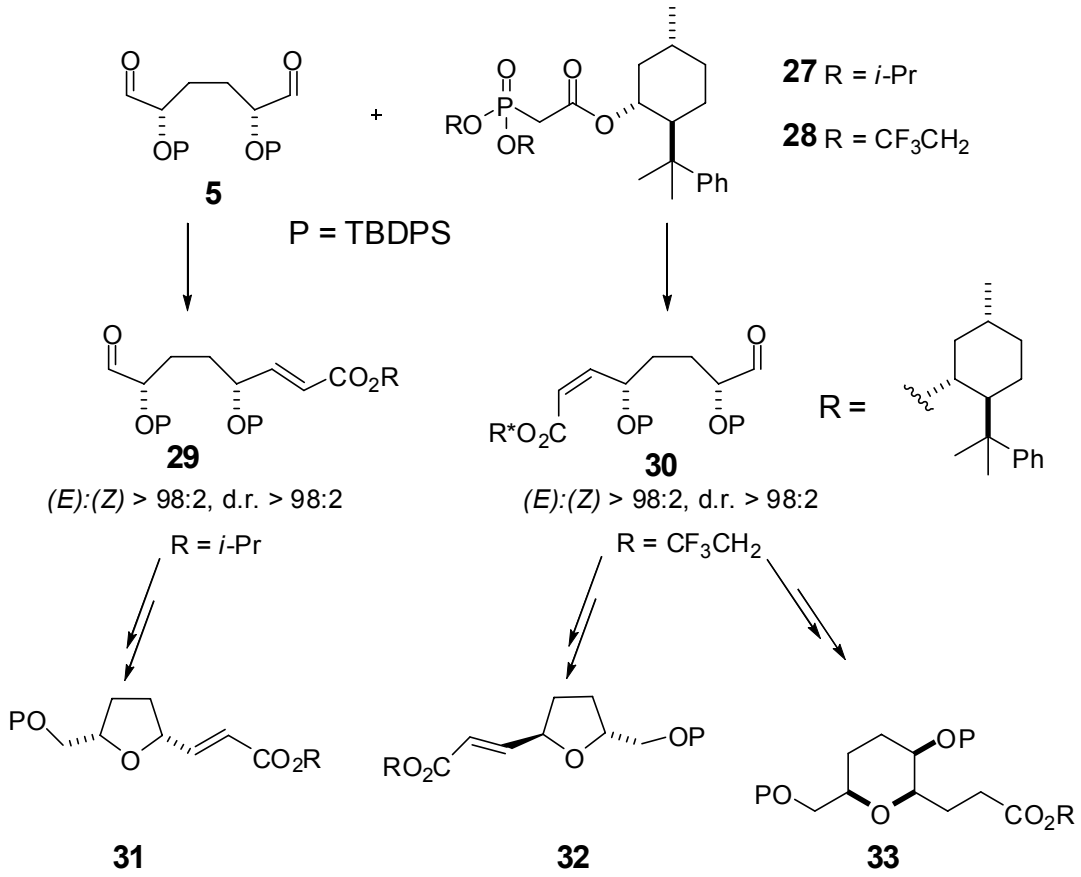


Figure 6: HWE reaction of **5** with **27** and **28**

The results from the experimental study (see Table 1) supported the predictions of the computational study. The reason for the diastereoselectivity is that only one face of the phosphonate enolate is accessible and attack from that face on either of the enantiotopic aldehyde groups leads to the same absolute configuration at the phosphonate stereocenter in the intermediate generated (Figure 7). The aldehyde face preferred for attack is dictated by the configuration at the α-carbon of the aldehyde group and this is rationalized based on the Felkin-Anh model.[89,90] Thus attack of the phosphonate on either of the two

enantiotopic aldehyde groups give intermediates (**34** and **37**) with opposite relative configurations at C3 and C4.

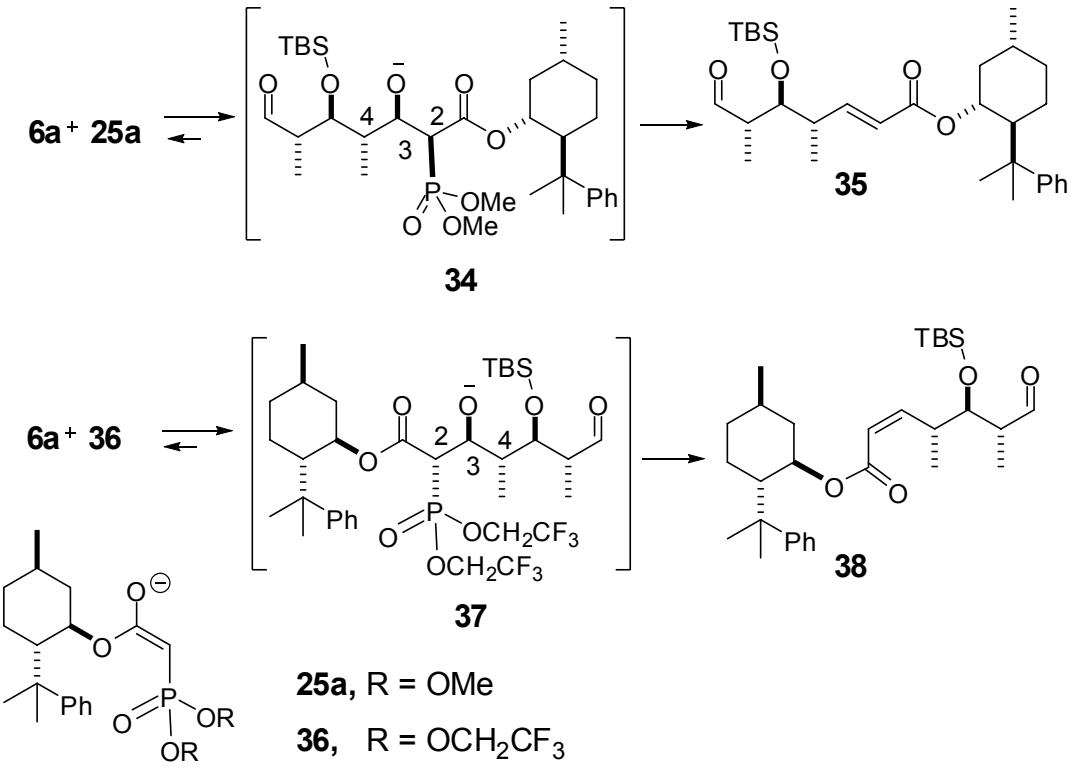


Figure 7: The transition states leading to the *E* and *Z* geometry.

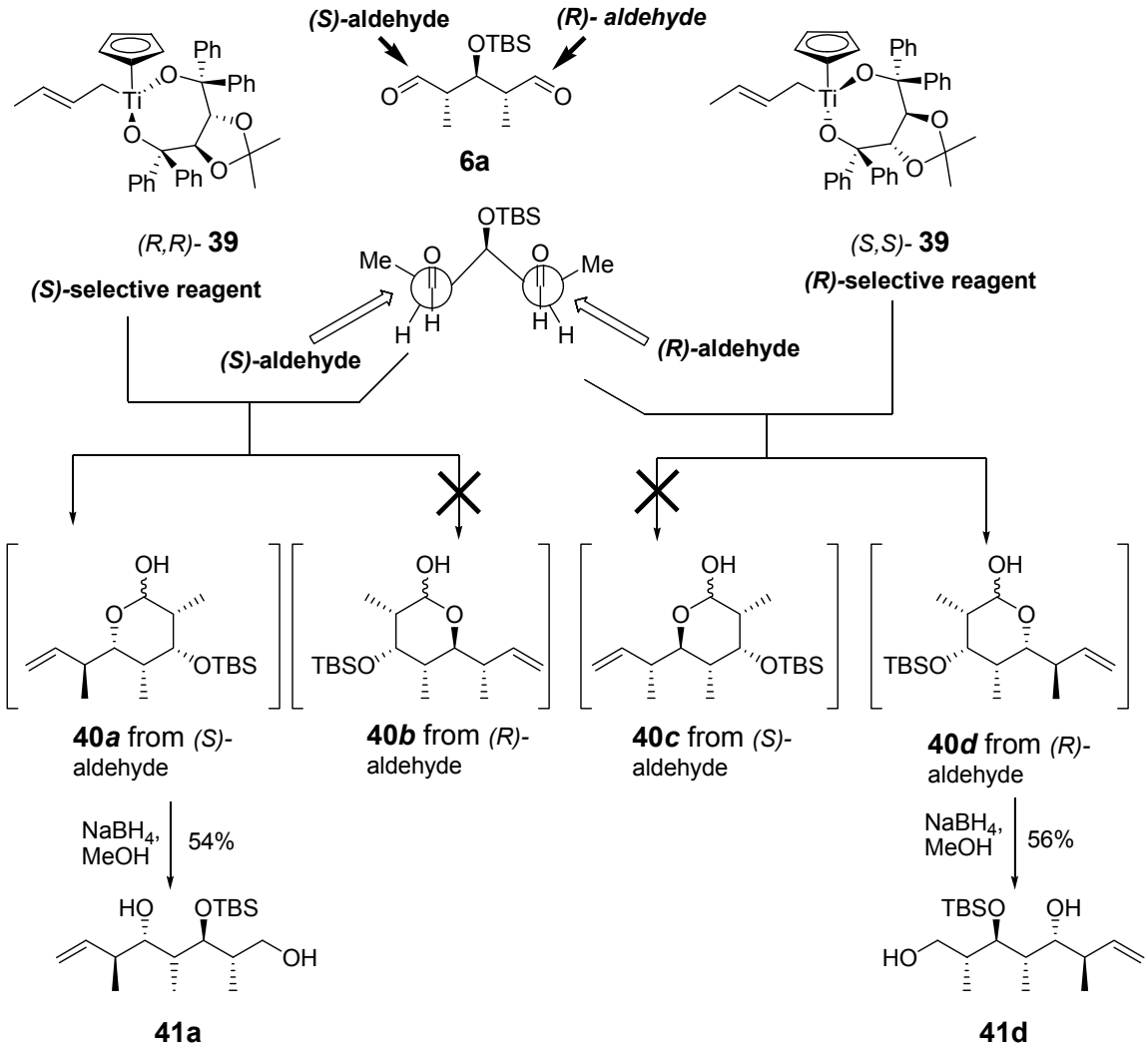
Structural analysis of the products obtained from the reaction indicates that the alkoxy group on the phosphonate under carefully chosen conditions influences the geometry of the alkene obtained from the reaction. Thus both the *E* and *Z* alkenes could be selectively prepared. This observation is more of a design feature, as it is known[86] from nonasymmetric HWE reaction that the geometry of the alkene produced can be controlled by the choice of the alkoxy group in the phosphonate reagent and reaction conditions.

To show the synthetic usefulness of their process, the alkenes obtained were converted into chiral tetrahydropyrans,[88] that are common fragments in natural products, by palladium catalyzed ring closing reaction[91] (Figure 6). The so-obtained tetrahydropyrans were used in the total synthesis of pyranicin[92] and

pyragonicin.[93] These natural products which are members of the non-classical subgroup of annonaceous acetogonins, exhibit a wide range of biological activities such as antimicrobial, pesticidal and do have strong cytotoxic properties.

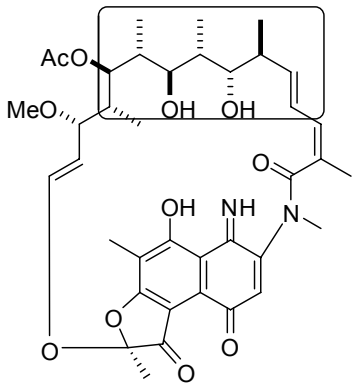
1.2.2.2 Enantiotopic group selection via asymmetric crotylation reaction.

The *meso* dialdehyde **6a** was also desymmetrized by BouzBouz and Cossy[46] via an asymmetric crotylation reaction using both enantiomers of chiral crotyltitanium complexes (*R,R*)-**39** and (*S,S*)-**39** developed by Hafner *et al* (Scheme 3)[94] The chiral crotyltitanium complexes **39** have previously been shown to have a high face selectivity in reactions with aldehydes[94] The (*R,R*)-**39** complex favors the *si* face of the aldehyde while the (*S,S*)-**39** enantiomer favors the *re* face. The high enantioface discrimination of this catalyst results from the interaction between the cyclopentadienyl ring and the bulky phenyl on the catalyst. The combination of the high face discriminating capability of the catalyst **39** and the high intrinsic 'Felkin' diastereoface selectivity of the aldehyde groups in **6a** accounts for the very successful asymmetric crotylation of **6a**.



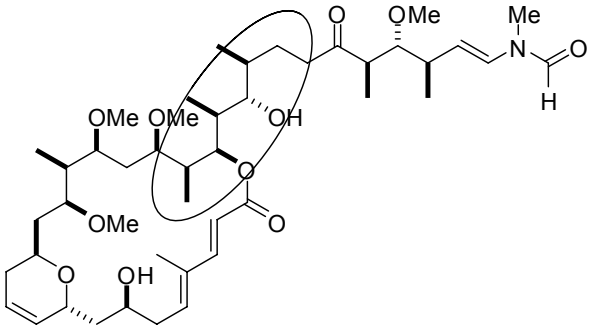
Scheme 3: Desymmetrization of *meso* dialdehyde **6a** via asymmetric crotylation.

Although the yields (54-60%) obtained from the reactions were moderate, the enantioselectivity was high enough for this method to be used in the synthesis of the C15-C24 fragment of (+)-discodermolide. The major product obtained from the reaction, which was isolated as the diol **41** after reduction with $NaBH_4$, contains a structural motif common to many natural products such as rifamycin S[7,8] and scytopycin[95,96] (Figure 8).



2

rifamycin S

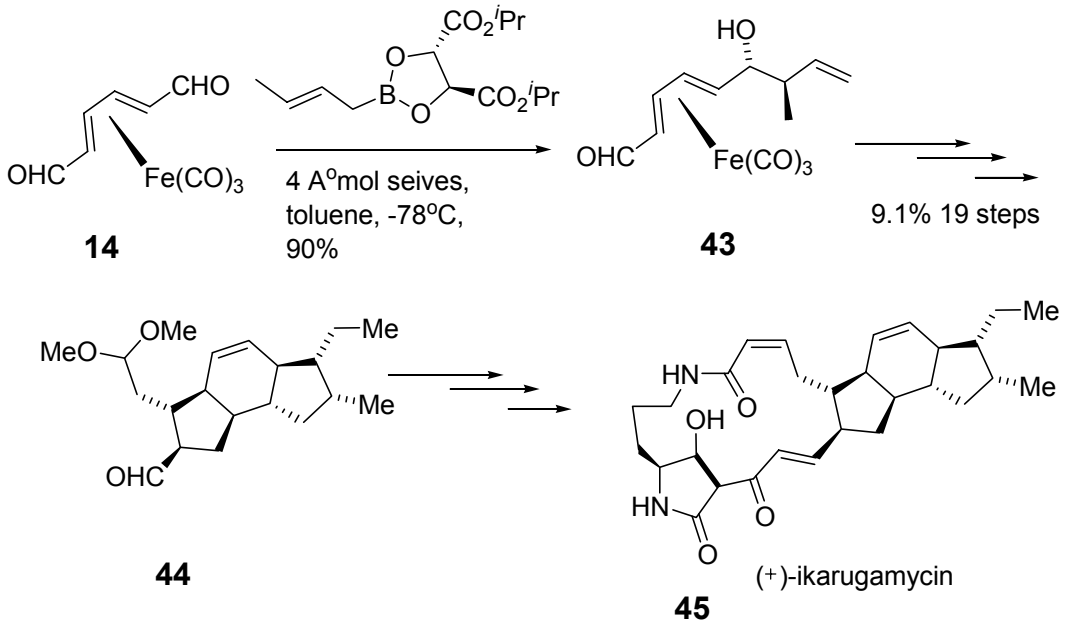


42

scytophycin C

Figure 8: Natural products which contain the stereopentad present in **41a** and **41d**

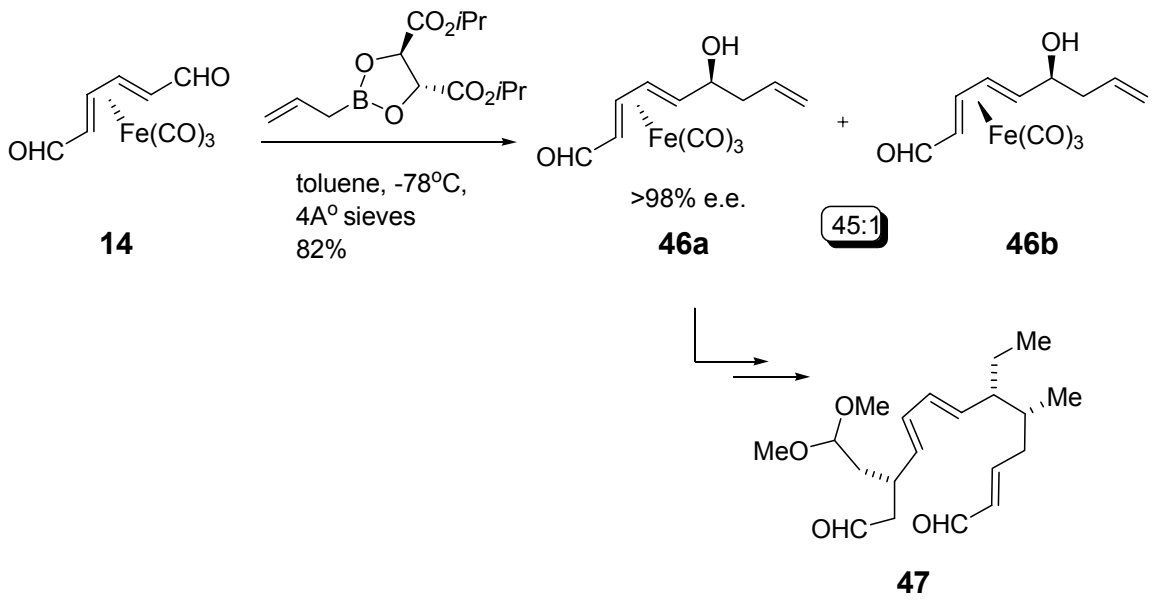
A crotylborinate derived from ethyl tartrate was successfully used in the desymmetrization of *meso* dialdehyde **14**.[81] Employing less than 1 equivalent of the chiral borinate reagent, Roush and Wada converted **14** to **43** in 90% yield and 98% ee. The product was converted to the *as*-indacene unit of ikarugamycin,[97] in 9.1% total yield in 19 steps (Scheme 4).



Scheme 4: Roush and Wada's formal synthesis of (+)-ikarugamycin

1.2.2.3 Enantiotopic group selection via asymmetric allylation reaction.

Roush and Park[81] also made use of an asymmetric allylation reaction to differentiate between the enantiotopic aldehyde groups of the *meso* dialdehyde **14**. Reaction of **14** with less than 1 equivalent of a tartrate derived chiral allyborinate furnished a 45:1 diastereomeric mixture of products with the major product **46a** having an ee of >98% (Scheme 5).

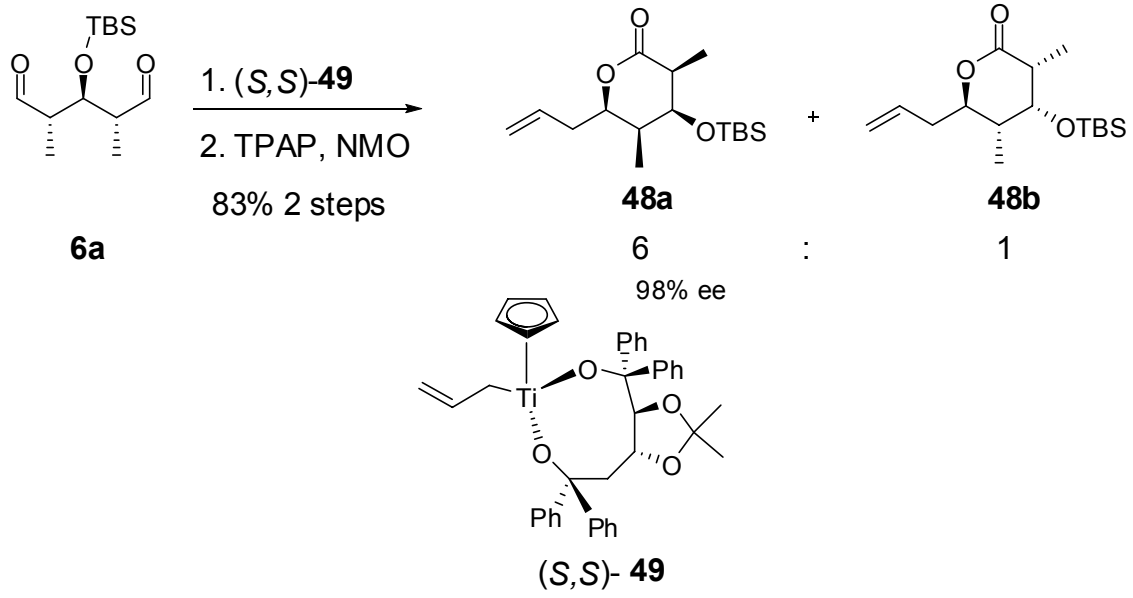


14 **46a** **46b** **47**

Scheme 5: Roush's allylborination of **14**.

The success of the reaction was attributed to electronic effects (dipole interactions) of the metal carbonyl ligand in the favored transition state of the allylborination. The product **46** is easily transformed to triene **47** for use in intramolecular Diels-Alder reactions to prepare functionalized six membered rings, which are common fragments in natural products.

BouzBouz and Cossy[46] also made use of an asymmetric allylation reaction to desymmetrize a meso dialdehyde. Employing **49**, the allyl derivative of the titanium complex used in the crotylation reation (Scheme 3), reaction with **6a** gave **48a** after oxidation with TPAP[98] (Scheme 6). The product **48a** is useful for the synthesis of numerous natural products.

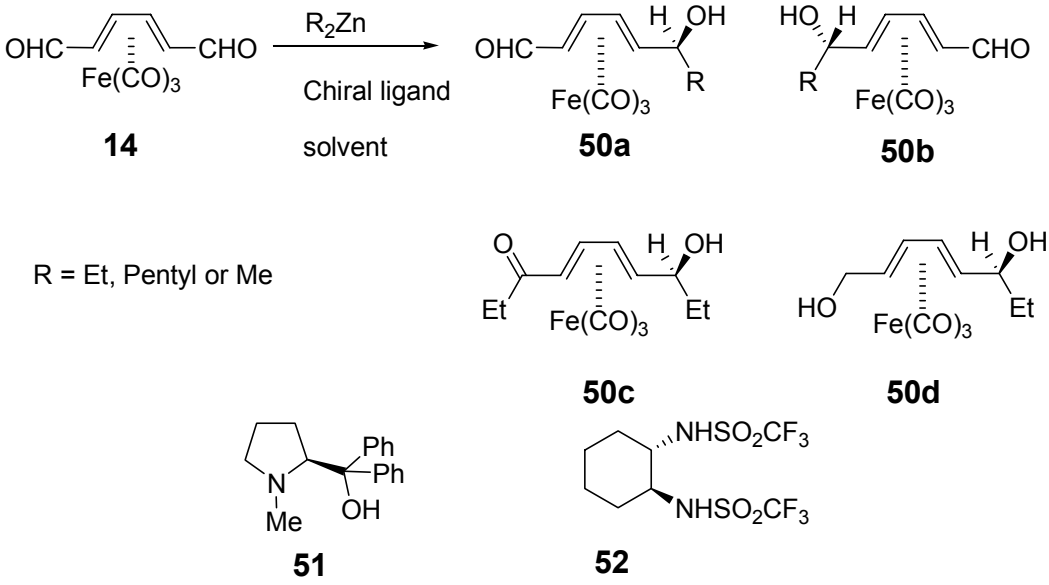


Scheme 6: Desymmetrization of *meso* dialdehyde **6a** via asymmetric allylation.

1.2.2.4 Enantiotopic group selection via asymmetric alkylation reaction.

The *meso* dialdehyde **14** was also desymmetrized by Takemoto *et al*[70,82,99] via an asymmetric alkylation reaction, using various dialkyzinc reagents in the presence of catalytic amounts of chiral ligands (Table 2). Optimization of the reaction conditions by changing the polarity of the solvent, temperature and mol % of ligand gave the mono alkylated compound **50a** in 78% yield and >98% ee for the diethylzinc addition. Applying the optimized condition for the ethyl addition to the reaction for the pentyl addition gave a similar result but to their surprise the alkylation using dimethylzinc was not successful. The yield and selectivity for the methylation was ultimately improved by changing the ligand and adding titanium isopropoxide.

Table 2 Catalytic asymmetric alkylation of meso $Fe(CO)_3$ complex **14** with dialkyzinc in the presence of chiral ligand **51**



14 **50a** **50b**

R = Et, Pentyl or Me

50c **50d**

51 **52**

entry	R_2Zn	ligand equiv	solvent*	time (hr)	yield of **50** **a**	**b**	**c**	**d**	**14**	e.e of **50a**(%)
1	Et	0.1	T-H (4:1)	4	59	1	7	-	9	94
2	Et	0.5	T-H (4:1)	1	78	3	2	-	9	>98
3	Et	0.5	M-H (4:1)	5	53	4	-	<1	28	>98
4	Et	0.5	E-H (4:1)	3	29	2	-	-	52	>98
5	pentyl	0.5	T	1.5	82	4	-	-	6	>98
6	Me	0.5	T-H (4:1)	2	17	2	-	-	57	86
7**	Me	0.03	T	1.5	71	7	-	-	12	86

* T-toluene, H-^{n}hexanes, M-methylene chloride, E-ether.

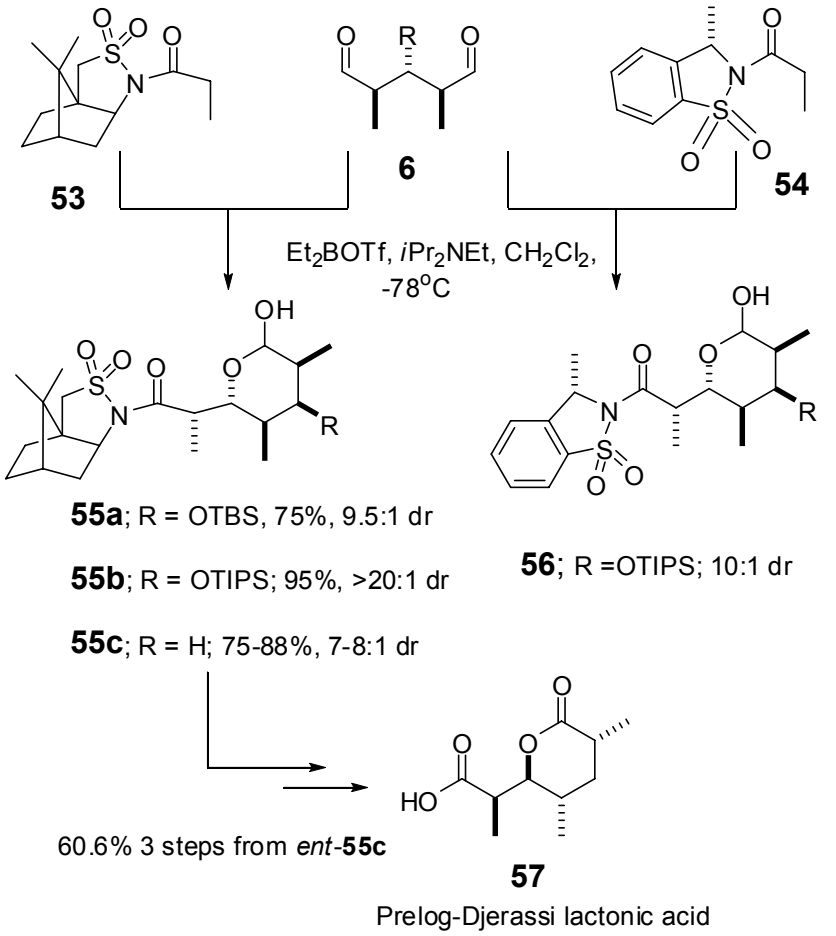
All reactions carried out at 0 ^oC with 2.5 equivalent of dialkyzinc reagent

** 1.8 equiv of 1:1 dialkyzinc: $Ti(^iOPr)_4$, ligand **52**,

1.2.2.5 Enantiotopic group selection via asymmetric aldol reaction.

De Brabander and co workers[68,75,77] made use of the aldol reaction to successfully desymmetrize the *meso* dialdehyde **6b**, a key step in their synthesis of denticulatins A and B.[68,75] As an extension to this chemistry, the *meso* dialdehyde **7** was similarly desymmetrized and the product was transformed to Prelog-Djerassi lactonic acid in 2 steps.[77]

For the process to be successful, the enolate of choice (which must be enantiomerically pure) must have only one face available for reaction (i.e. one of the faces must be shielded by the chiral auxiliary). Employing the *Z*(O)-borylenolates generated from the enantiomerically pure chiral sultam **53** or **54**, the *meso* dialdehydes **6a**, **6b** and **7** were successfully desymmetrized to afford 2:1 epimeric mixtures of the lactols **55a**, **55b, 55c** and **56** (Scheme 7).



Scheme 7: De Brabander's desymmetrization via aldol reaction.

The success of the reaction was attributed to three factors, the chiral sultam borylenolate[100,101] diastereoface selectivity, the high intrinsic "anti-Felkin" aldehyde diastereoface selectivity and the aldol relative topicity dictated by the *Z* geometry of the enolate. In the transition state leading to the observed product (Figure 9), the *R*-aldehyde group readily aligns to the less hindered face of the enolate and in an 'anti Felkin'. Although the *S*-aldehyde group can equally align to the less hindered face of the enolate, this pathway is less favored because it can only do so in a 'Felkin' mode leading to a gauche pentane interaction between the methyl groups of the aldehyde and the enolate moieties. The combination of these three factors allows for the transition state leading to the "anti-Felkin" product, to be considerably lower in energy when compared to the

one leading to the “Felkin” product and as such the selectivity observed from the reaction.

Oxidation of the lactols using bromine or TPAP[98] gave the corresponding lactones that were crystalline, allowing for both the relative and absolute configuration of the products to be unequivocally assigned by X-ray crystallography. The lactone obtained from the oxidation of lactol *ent*-**55c** was converted to the Prelog-Djerassi lactonic acid **57** after hydrolysis of the chiral auxiliary.[77]

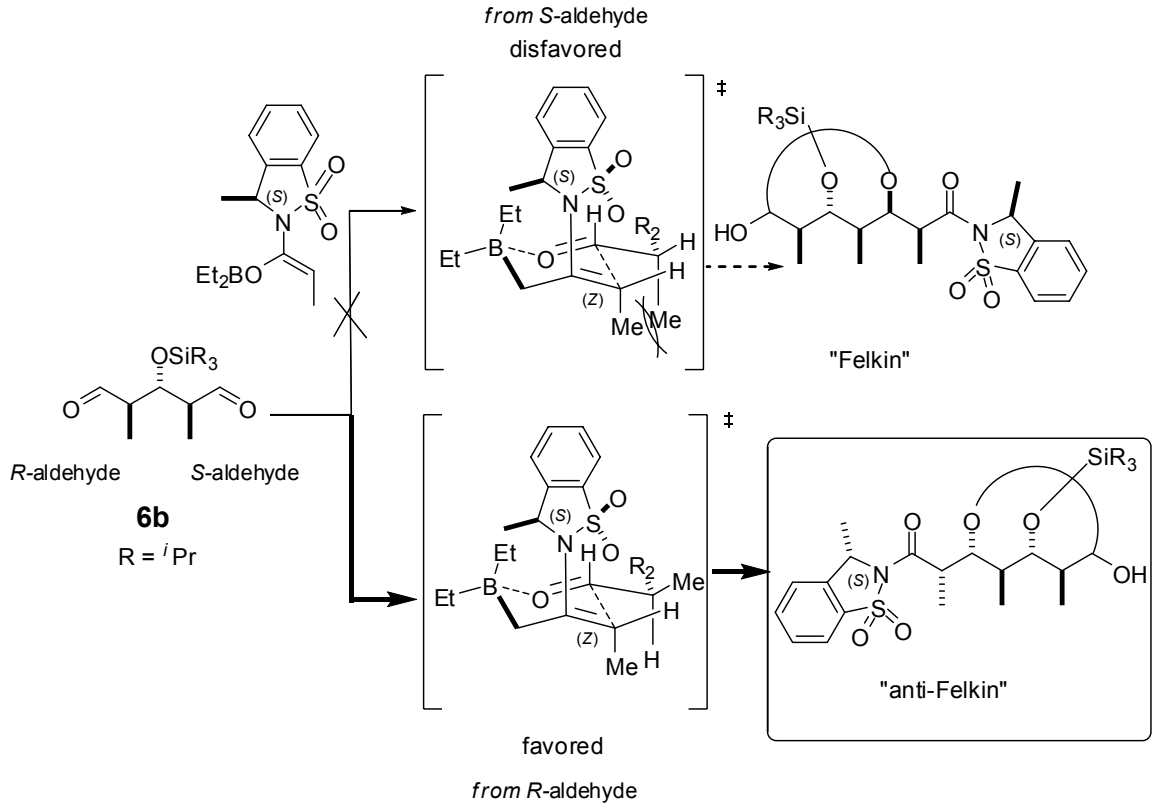
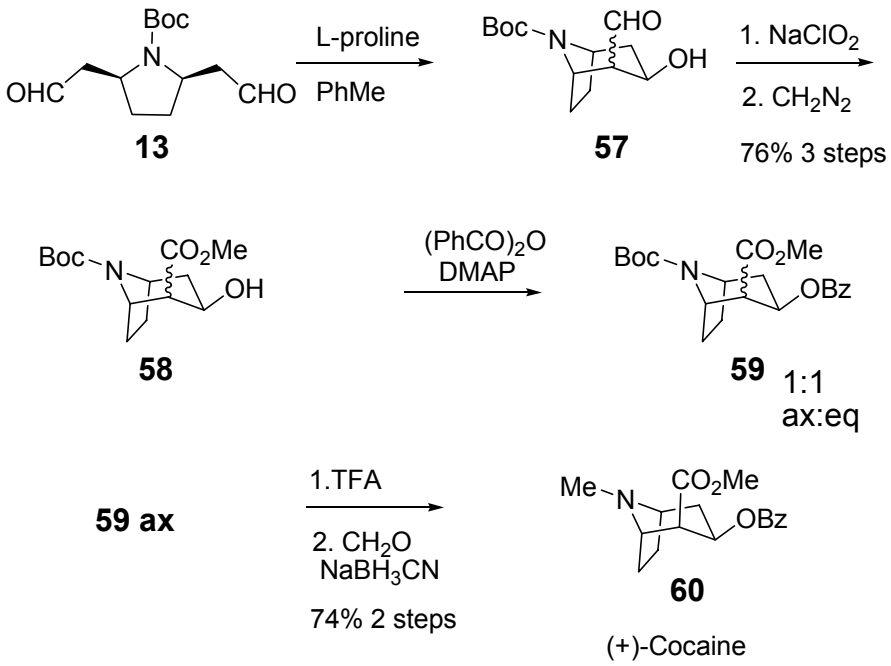


Figure 9: Transition state model to explain the selectivity of the aldol product.

Pearson and Mans[78] made use of an intramolecular enol-*exo*-aldol reaction to desymmetrize the cyclic meso dialdehyde **13** as a key step in their synthesis of the unnatural (+)-cocaine. The meso dialdehyde **13**, obtained from commercially available material in *ca*. 20% yield over 9 steps (see section 1.2.2),

was subjected to an intramolecular aldol reaction mediated by L-proline to furnish a 1:1 mixture of *ax:eq* bicyclic hydroxyl aldehydes **57** (Scheme 8).



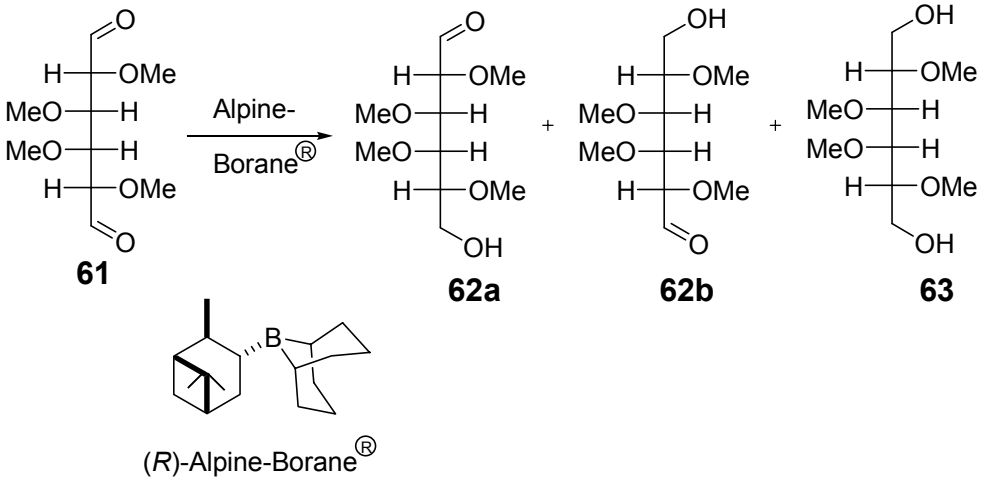
Scheme 8: Pearson and Mans synthesis of cocaine.

Attempts to improve the selectivity of the reaction by changing the reaction solvent, reaction time, or temperature were not successful. The 1:1 mixture of the isomers obtained was subjected to oxidization, esterification, deprotection and alkylation of the resulting amine to furnish the (+)-cocaine in 86% ee and 6.5% over all yield from the commercially available alcohol.

1.2.2.6 Miscellaneous reactions.

Ward *et al*[102] utilized an asymmetric reduction reaction to desymmetrize a meso dialdehyde during their study of asymmetric reactions with modest group selectivity. The meso dialdehyde **61** was prepared from methyl α-D-galactose in 7 steps. Reduction of **61** with 3 equivalents of either enantiomer of Alpine-Borane® (**64**) gave a mixture of products (Table 3) with increasing ee as the conversion increases.

Table 3: Reduction of **61** with Alpine-Borane ®



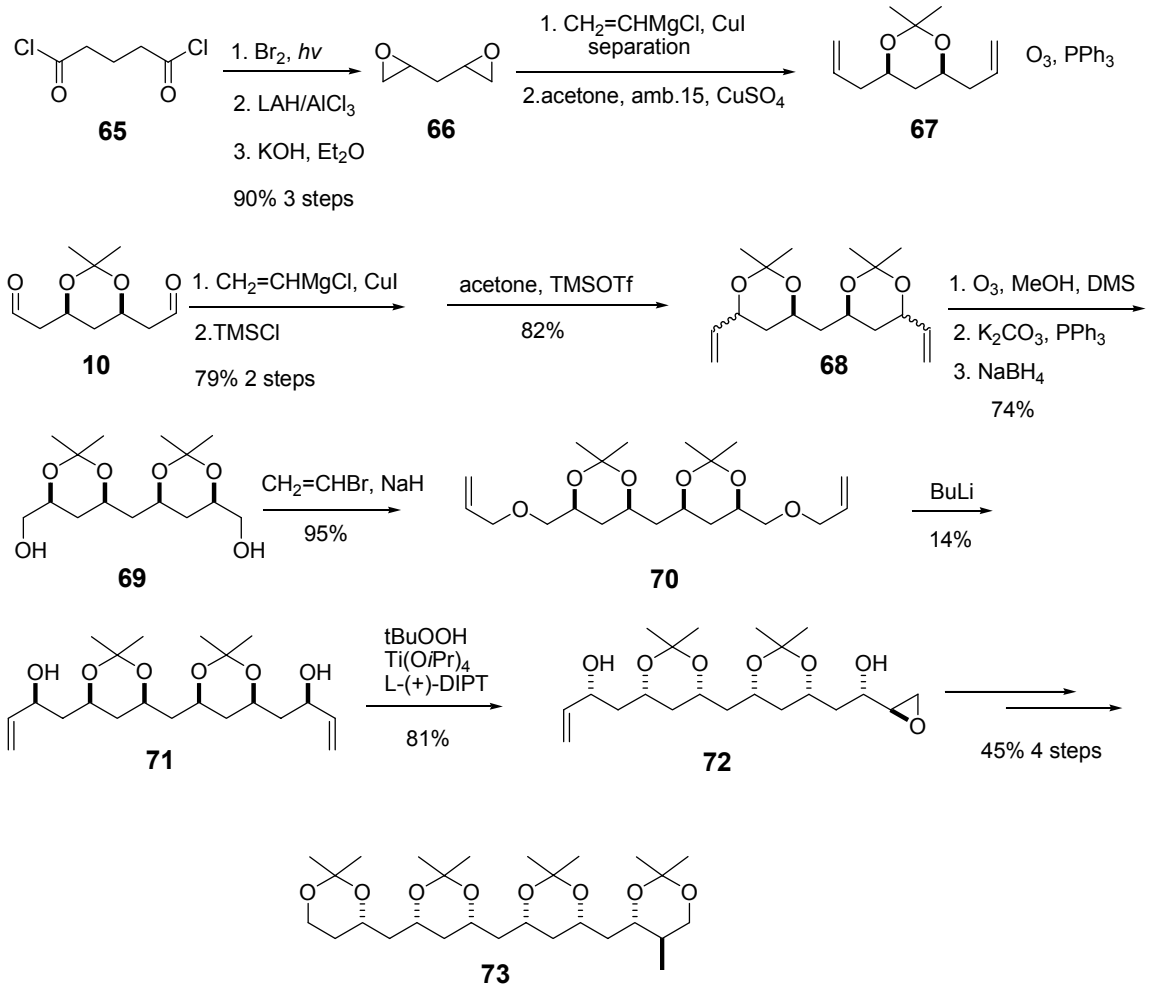
Reagent	Temp (°C)	Time (h)	%Yield (**63**)	%Yield (**62a**+**62b**)	Selectivity **62a:62b**(ee)
(R)	-78	1	32	52	3.5:1(55)
(R)	-78	2	46	43	7:1(75)
(R)	-78	4	70	23	13:1(86)
(*S*)	-78	2	46	44	1:7(75)
(R)	-95	3	43	46	12:1(85)
(R)	-95	4	50	42	15:1(87)
(R)	-95	5	59	34	18:1(89)

1.2.3 Simultaneous two directional chain elongation followed by desymmetrization.

Simultaneous two directional chain elongations constitute an approach for rapidly accessing symmetrical long chain backbones with numerous stereogenic centers. Depending on the type of reaction utilized up to four new stereogenic centers are generated in one operation. If the terminal functional groups on the products generated from such reactions can be differentiated, stereochemically complex enantiomerically pure fragments could be synthesized rapidly. The use of *meso* dialdehydes in this approach from three research groups is discussed below.

1.2.3.1 Schreiber's bis-Grignard addition.

Schreiber and Goulet[103] in their synthesis of the polyol fragment of mycoticin A[76] provided the first example of the use of *meso* dialdehydes in a simultaneous two directional chain elongation approach (Scheme 9). The *meso* dialdehyde **10** was prepared from commercially available glutaryl dichloride in six steps. A non-stereoselective two-directional Grignard addition of vinlymagnesium chloride to the *meso* dialdehyde furnished a diol which was subjected to a modified Noyori's[104] protocol for acetal formation to give compound **68**. Ozonolysis of **68** followed by isomerization of the dialdehyde obtained afforded the thermodynamically favored *meso* diol **69** after reduction of the aldehyde groups. Bisallylation of the diol **69** followed by 1,2-Wittig rearrangement gave *meso* **71.** The terminal allylic alcohol groups in **71** were differentiated by Sharpless[105] asymmetric epoxidation to afford the enantiomerically pure polyol derivative **72** (Scheme 9). Further elaboration of **72** gave **73** that did not match the degradation product obtained from mycoticin A and established that the polyol fragment of the natural product did not possess the all *syn* configuration.

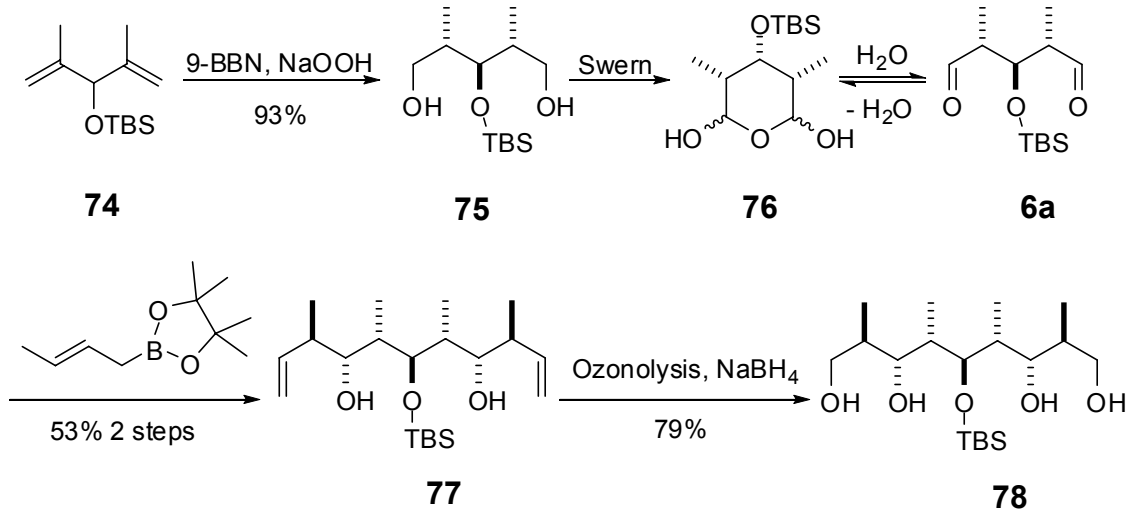


Scheme 9: Schreiber's synthesis of the polyol fragment of mycoticin A

1.2.3.2 Harada's crotylation addition

Harada *et al.*[8] utilized the *meso* dialdehyde **6a** in their synthesis of the tetrapropionate fragment of rifamycin S. The dialdehyde **6a** was prepared from bis-hydroboration of dialkenyl carbinol derivate **74** to furnish the diol **75** that was subjected to Swern oxidation[106] to afford the dialdehyde as an equilibrium mixture with the hydrate form (Scheme 10). Employing the crotyl-borination reaction developed by Roush *et al.*[107] to carry out a simultaneous two directional addition to the dialdehyde **6a** afforded the *meso* diene **77** as a 7.5:1 ratio of stereoisomers. The mono addition product was also isolated in 8% yield. The

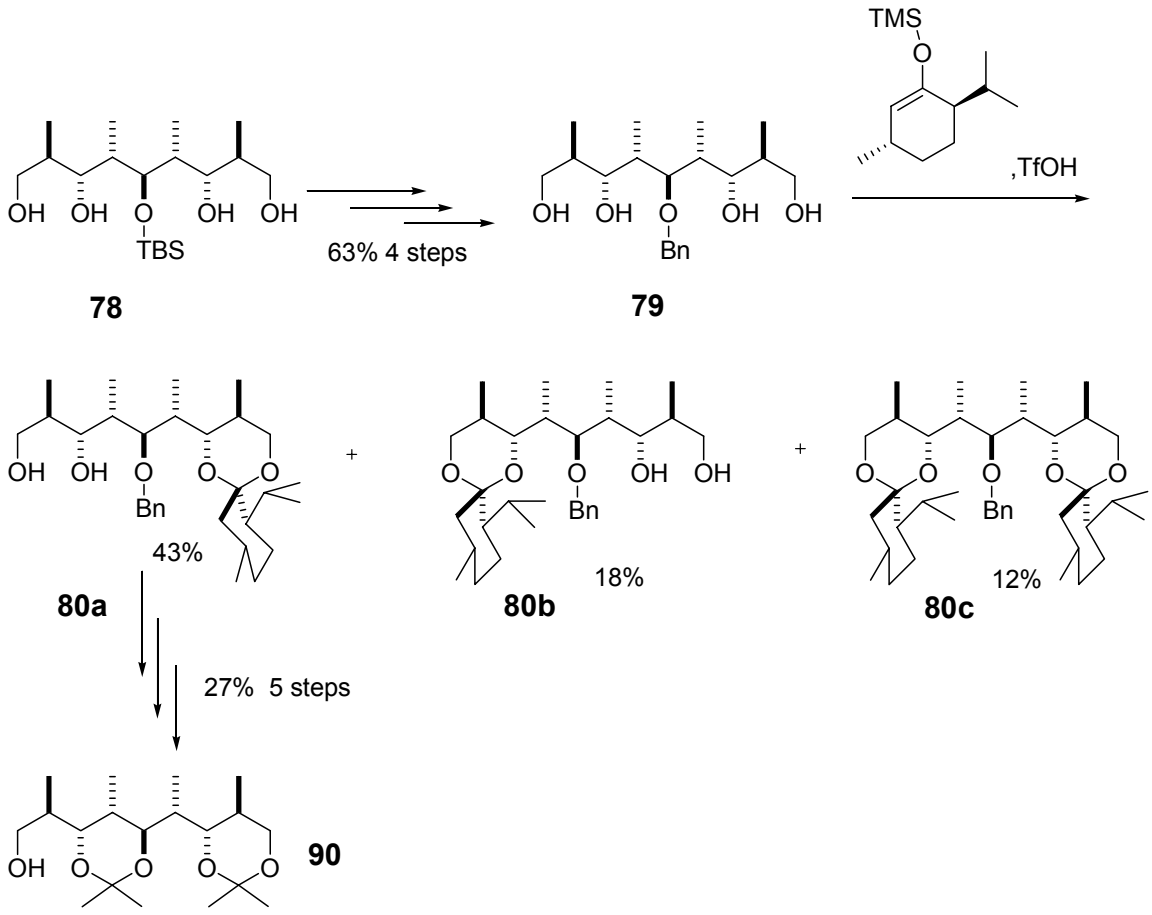
meso tetrol with seven stereogenic centers was obtained after ozonolysis and reduction.



Scheme 10: Preparation of meso tetrol **78.**

Two related methods were employed to differentiate the terminal alcohol groups of the tetrol **78**. The first approach involved selective cyclic acetal formation[8,74,108] on one end of the tetrol using a chiral ketone derivative and the second involved selective acetal cleavage[73,109] on a bis acetal derivative of **78**. In the first approach, to avoid the participation of the TBS protecting group in the acetal formation reaction, that group was exchanged for a more stable benzyl group in a four step sequence. A more direct approach using the benzyl protected derivative of **74** from the beginning was problematic on scale up during separations of the stereoisomers in the both the hydroboration and crotylboration steps. Differentiating the enantiotopic diol groups in **78** via acetal formation under kinetic control using the silyl enol ether derivative of *d*-menthone afforded a 4.5:1 mixture of mono protected compounds **80a** and **80b** in 61% isolated yield (Scheme 11). The bisacetal **80c** and starting materials were also isolated in 12% and 10% respectively. Protection of the primary alcohol in **80a**, followed by hydrolysis of the menthonide group, de-benzylation,

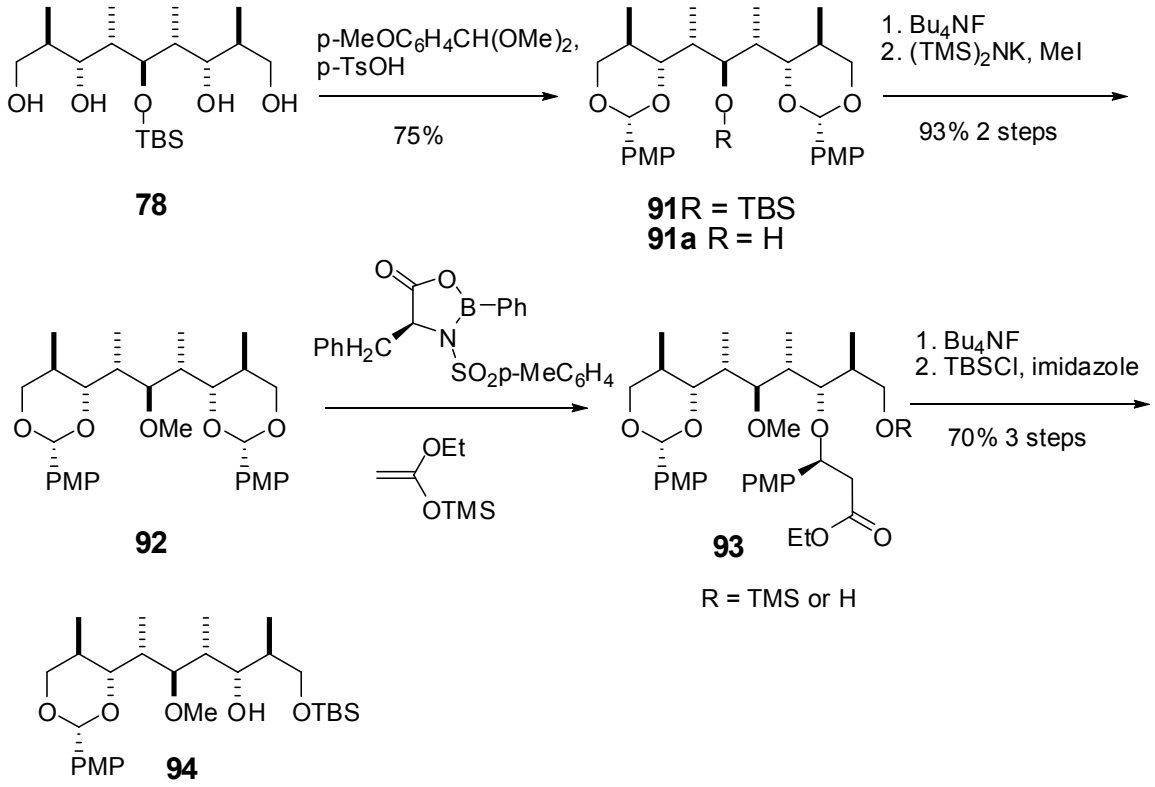
and protection of the tetrol as the bis acetonide afforded the desymmetrized **90** in >95% ee.



Scheme 11: Desymmetrization by acetal formation.

The second approach involved enantioselective ring cleavage of bis-acetal **92**. The cleavage was carried out with a nucleophile in the presence of an oxazaborolidinone as the chiral mediator[110] (Scheme 12). A combination of different oxazaborolidinone and nucleophiles were screened on a model compound to find the best conditions. The TBS derivative **91** was too hindered and unreactive under the optimized condition for the cleavage while the ee obtained from the free hydroxyl derivative **91a** was very poor (3% ee). The latter result was attributed to unselective activation of the inside “oxygen” of the acetal

group by Brønsted acid generation from the coordination of the oxazaborolidinone to the hydroxyl group.[111]



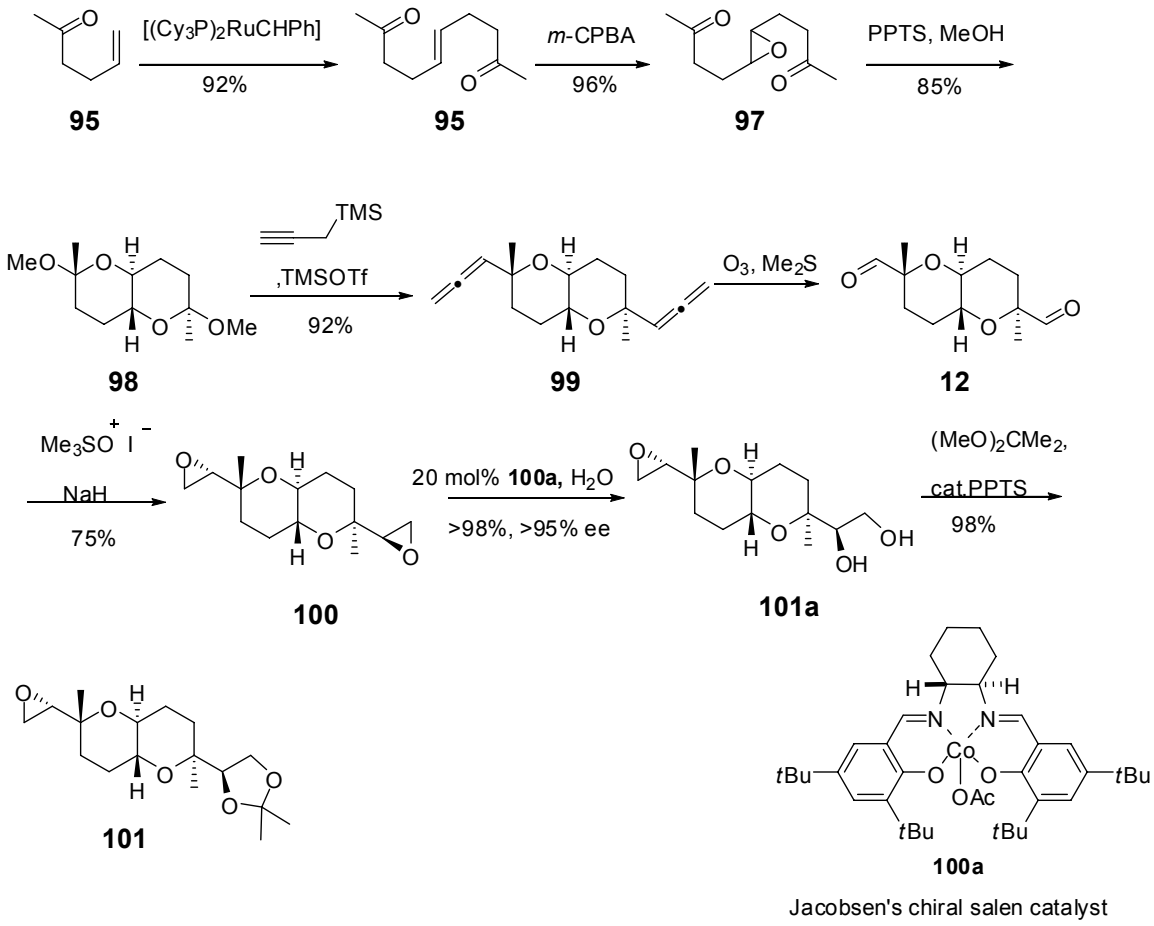
Scheme 12: Desymmetrization of **74** by enantioselective ring cleavage.

The use of the less hindered methyl ether derivative **92** gave **93** as a mixture of the free hydroxyl and TMS protected mono cleaved primary alcohol as a 9:1 ratio of stereoisomers. The nucleophile moiety was cleaved to afford a diol that on protection of the primary alcohol afforded the desymmetrized compound **94** in 87% ee and 70 % overall yield from **92**.

1.2.3.3 Nelson's diepoxidation.

Nelson and co-workers[71] desymmetrized the centrosymetric *meso* dialdehyde **12** in their formal synthesis of hemibrevetoxin B (Scheme 13). The key intermediate **101** was prepared in >95%ee in 34% overall yield in 8 steps

which is a marked improvement on the 14% overall yield from 22 steps previously reported.[112]



Scheme 13: Nelson's synthesis of the core fragment of hemibrevetoxin B.

The key step in the synthesis of meso dialdehyde **12** was the PPTS catalyzed cyclization of the epoxy diketone fragment **97** to give the thermodynamic product **98**. Nucleophilic substitution on **98** with trimethylsilylpropyne followed by ozonolysis gave the C_i symmetric dialdehyde **12**. Bidirectional sulfur ylide-mediated epoxidation of **12** gave a 20:1 mixture of *meso* to chiral bisepoxides **98**. Desymmetrization of the *meso* diepoxide was accomplished via enantioselective epoxide hydrolysis mediated by Jacobsen's chiral salen catalyst[113] to give **101** after acetonide protection of the diol.

1.2.3.4 Miscellaneous reactions.

Although Hoffmann's use of a *meso* dialdehyde in a simultaneous two directional reaction did not include the differentiation of the enantiotopic terminal groups, it is still worth mentioning in this section because of the reaction type involved. A simultaneous two directional Mukaiyama[114] aldol reactions of *meso* dialdehyde **11** with **103** and **104** gave the bis addition adducts **105** and **106**, respectively. The diastereoselectivity of the Mukaiyama aldol reactions favored the *meso* isomers (5:1) and was achieved using a non-chelating Lewis acid as precedented by Evans *et al*[115,116] Compounds **105** and **106** (Figure 10) were prepared as part of a conformational analysis study on *oligo*-1,3-dioxanlymethanes[117] and bis(1,3-dioxan-5-yl)ethane derivatives.[118]

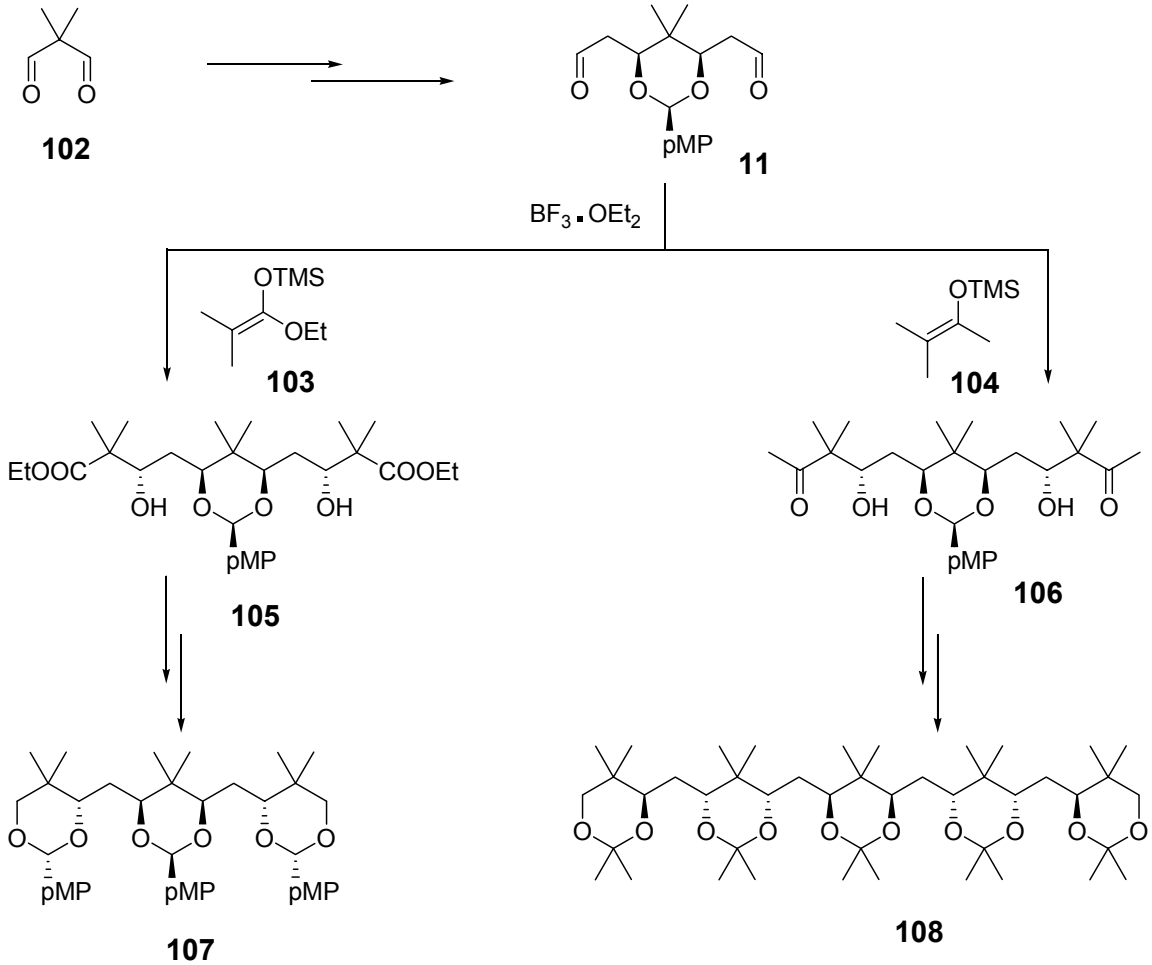


Figure 10: Hoffmann's simultaneous two directional aldol additions.

Chapter 2

Results and discussion

2.1 The thiopyran route to polypropionates

The use of cyclic sulfides as templates to synthesize naturally occurring compounds of biological importance has been well documented over many year's.[1,119] The use of thiopyran derivatives to rapidly generate polypropionate fragments has been an ongoing research theme within the Ward group.[20-22,120] A structural motif common to many polypropionate derived natural product is a hexapropionate unit and as such the strategy of Ward to couple tetrahydro-4*H*-thiopyran-4-one **112** and it's 3-carboxylaldehyde derivative **110** to give hexapropionate synthons in 2 aldol reactions is a very attractive process (Figure 11). The strategy is of more interest due to the possibility of generating six stereogenic centers in two carbon-carbon bond-forming reactions. The relative ease of preparation of the fragments from the same commercially available material is an added advantage in this route.

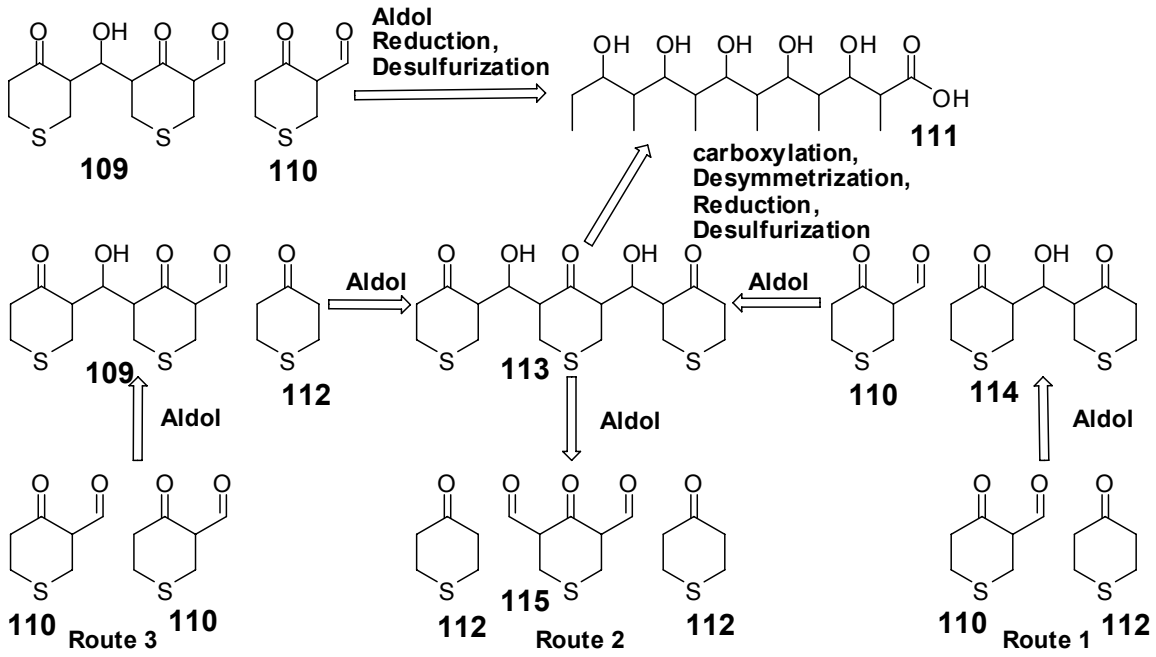
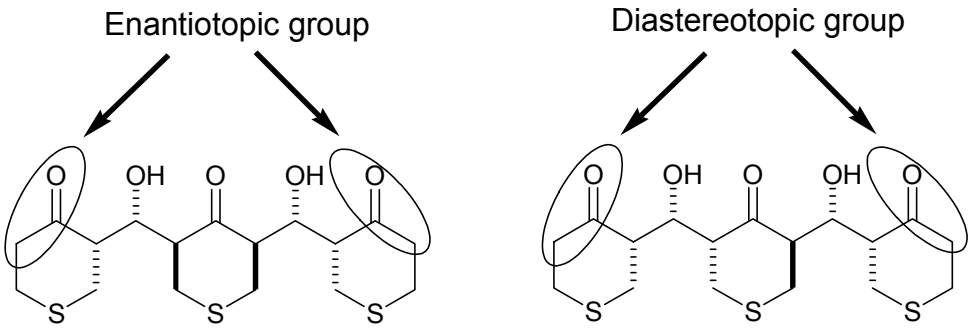


Figure 11: Retrosynthetic analysis of a hexapropionate using the thiopyran route.

Another interesting feature of this strategy concerns group selective reactions[121] on the bifunctional hexapropionate synthons. Enantiotopic and diastereotopic group selective reactions are required for *meso* and chiral hexapropionate synthons, respectively. An advantage of the thiopyran template is that the functional groups to be differentiated are in a cyclic structure and the resulting rigidity allows for various reactions to be rationally investigated (Figure 12).



meso hexapropionate synthon chiral hexapropionate synthon

Figure 12: Thiopyran based hexapropionate building blocks with enantiotopic and diastereotopic groups.

Within the thiopyran route to hexapropionates, three different pathways were identified for exploration (Figure 11). The first route involves the aldol addition of ketone **112** to a stable protected aldehyde fragment to afford a tetrapropionate building block that can either be appropriately functionalized to give a tetrapropionate unit or can be coupled with another aldehyde **110** to give a hexapropionate building block (Figure13). This route, which has been extensively studied within the group[20,21], is termed sequential two-directional aldol reactions.

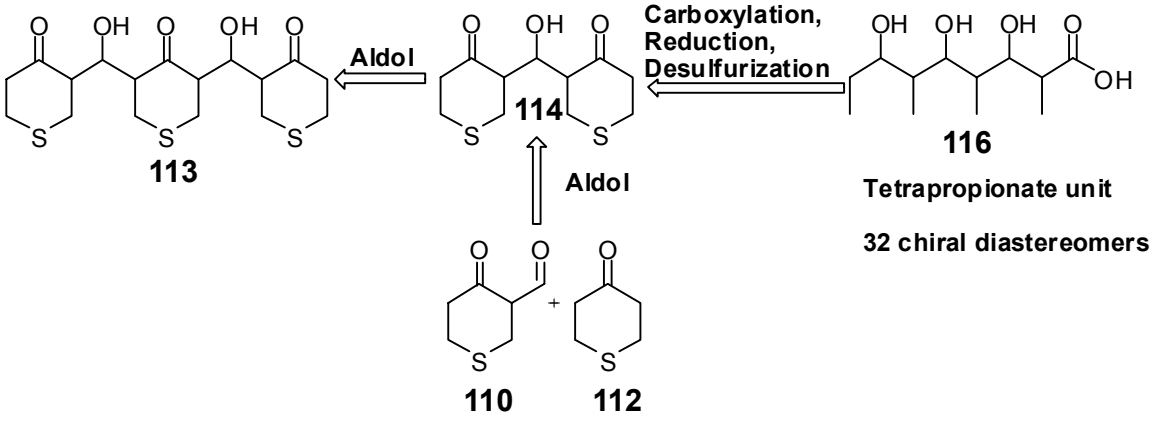
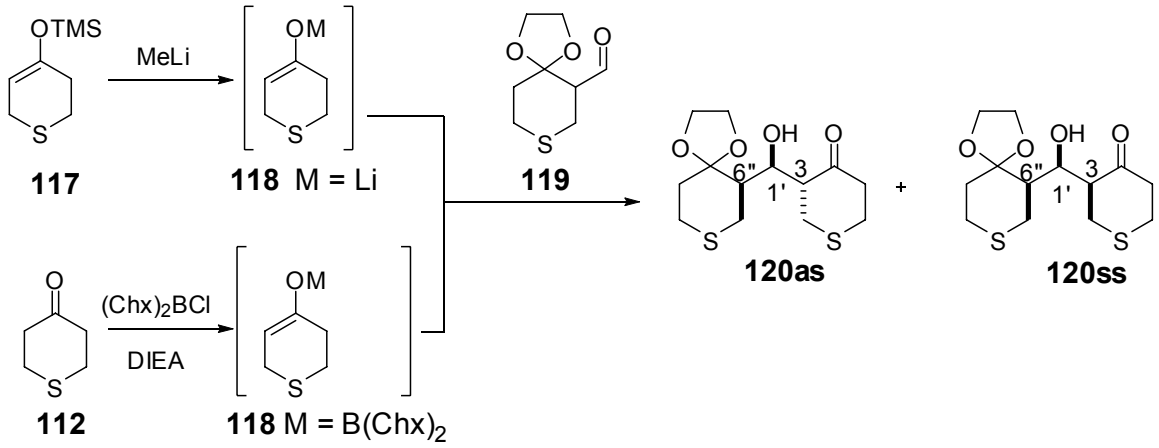


Figure 13: Retrosynthetic analysis on sequential two directional aldol additions

Aldol reactions of the ketal protected racemic aldehyde **119** with different enolates generated from **112** can generate 4 different diastereomeric products. The use of the lithium enolate **118** (M = Li) generated under 'amine' free conditions[20,21] and the boron enolate **118** (M = $B(Chx_2)$), afforded the 1',3-*anti*-1',6''-*syn* 'Felkin' aldol adduct **120as** as the major product in 70% (9:1 dr) and 84% (15:1 dr) isolated yields, respectively (Scheme 14).[20,22]



Scheme 14: Aldol addition of different enolates of **112** to **119**.

The aldehyde face selectivity in these reactions was accounted for using the Evans'[116] proposed merged effects of 1,2 and 1,3 asymmetric induction and the aldol relative topicity follows the Zimmerman-Traxler[122] 'closed' transition state model (Figure 14).

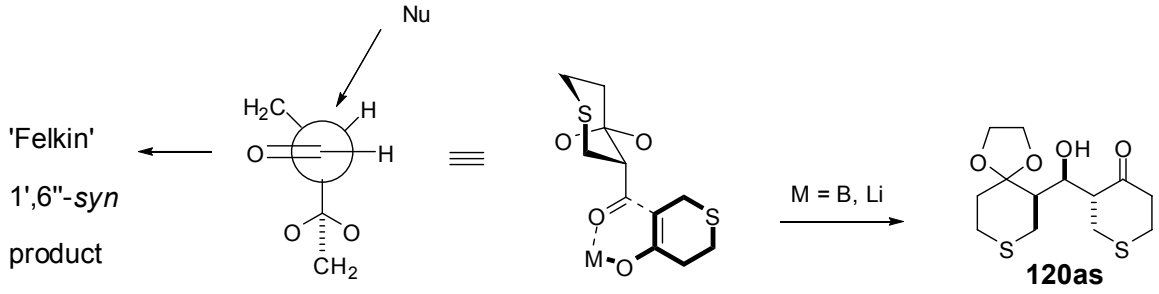


Figure 14: Transition state model explaining the diastereoselectivity of aldol reaction of Li and B enolates of **112** with **181**

The 1',3-*syn*-1',6''-*syn* 'Felkin' aldol adduct **120ss** was obtained in 87% yield (16:1 dr) from the reaction of the silyl enol ether **117** with the aldehyde **119** promoted by $TiCl_4$ (Figure 15). The same model proposed above was used to justify the aldehyde face selectivity while the aldol relative topicity was accounted for via the 'open' transition state model generally invoked in Mukaiyama[114] type aldol reactions.

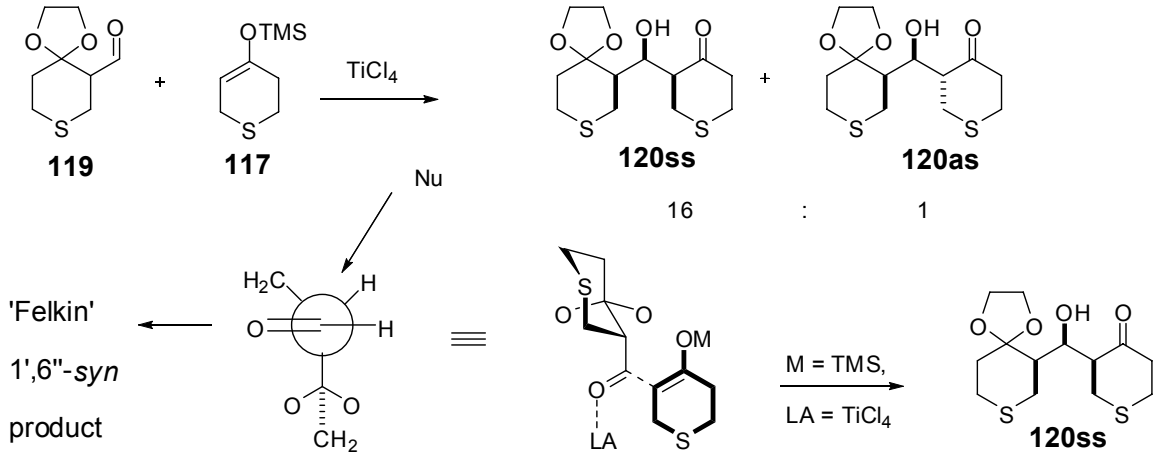


Figure 15: Mukaiyama type aldol reaction of **119** with **117**.

In contrast to the reactions in Figure 14 and 15 that gave the 'Felkin aldol adducts **120as** and **120ss**, the $MgBr_2 \cdot Et_2O$ mediated reaction of **119** with **117** gave exclusively the 'anti-Felkin' adducts **120sa** and **120aa** in 84% isolated yield in a 3:1 dr (Figure 16). The diastereoselectivity of the reaction was rationalized by assuming the reaction proceeds via a chelated intermediate and attack from the least hindered face and an 'axial' approach of the nucleophile reinforces one another.

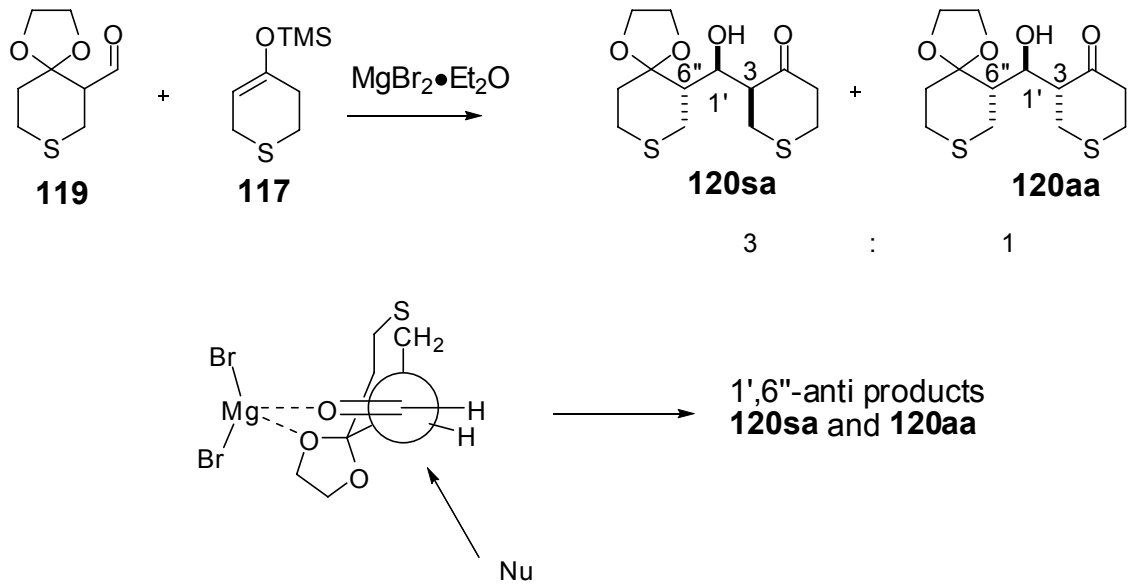
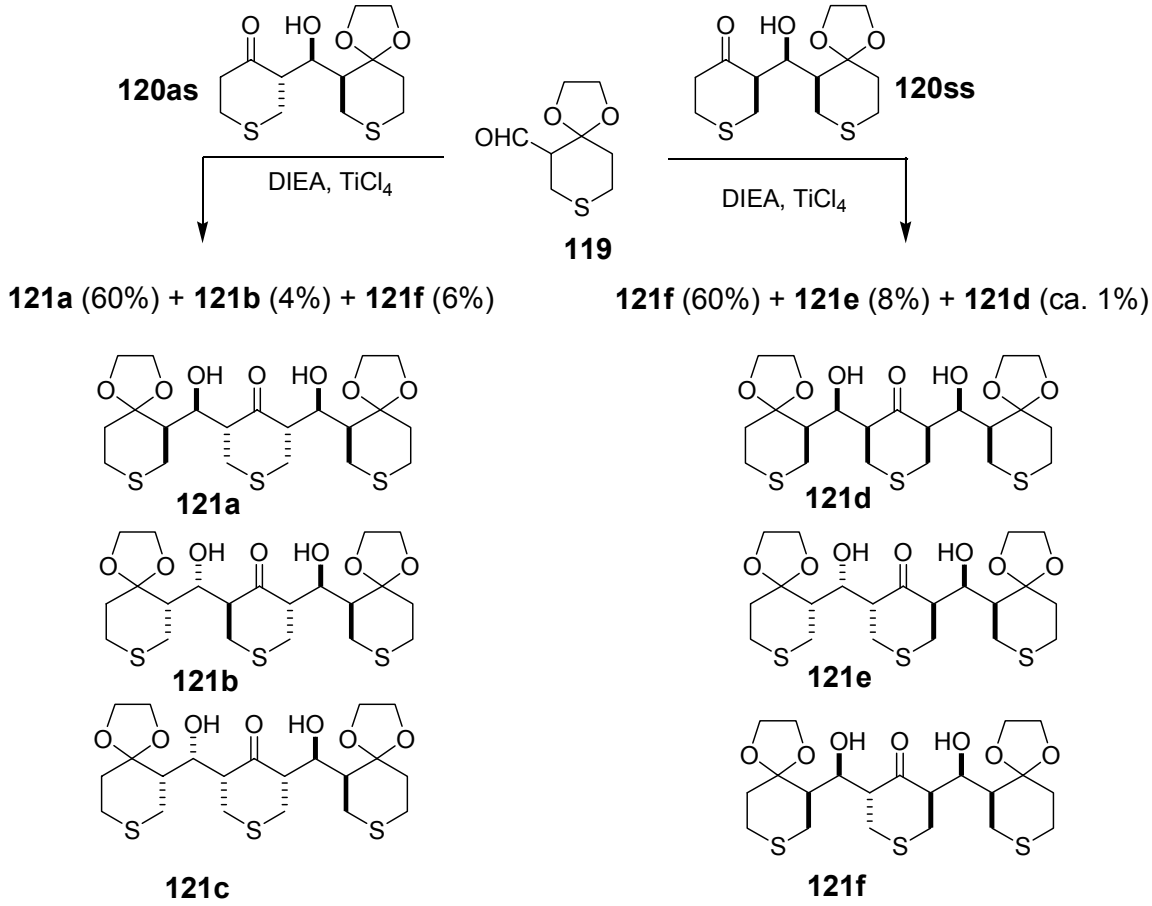


Figure 16: $MgBr_2$▪Et_2O mediated aldol reaction of **119** with **117.**[22]

The aldol adducts **120as** and **120ss** were used in a second aldol coupling to furnish bis aldol products. Titanium enolates generated from the reaction of the aldol adducts **120as** and **120ss** with $TiCl_4$ in the presence of DIEA were reacted with aldehyde **119** to give mixtures of bis aldol adducts **121** (Scheme 15).



Scheme 15: Second aldol coupling.

The second proposed route (Figure 11) involves a “one pot” simultaneous two directional aldol addition of the ketone **112** to the thiopyran derived dialdehyde **115** to afford a hexapropionate building block. The use of a *meso* dialdehyde **115** should lead to easy preparation of *meso* hexapropionate fragments that in turn could be desymmetrized by appropriate enantiotopic group selective reactions. One aim of this research was to identify and synthesize a practical *meso* thiopyran based dialdehyde and find conditions for simultaneous aldol couplings with ketone **112** to afford meso hexapropionate building blocks. A major challenge within this study has to do with the fact that 4 new stereogenic centers are generated in the reaction and as such 10 possible

diastereomers could be formed. The objective was to conduct the reaction in a stereocontrolled fashion.

The third identified route (Figure 11) involves the coupling of a suitable β–keto-carbonyl fragment to the protected keto-aldehyde derivative of **110** to afford a tetrapropionate unit **109** in one step. Alternatively, after appropriate functional group manipulations, a second coupling of **109** with **110** would give a hexapropionate unit in a sequential one directional fashion (Figure 11, route 3). Two main challenges exist in this route: the choice of a suitable synthetic equivalent for β–ketoaldehyde **110** that must react stereoselectively and regioselectively at the γ-position (i.e the fragments must be capable of undergoing a vinylogous[123] aldol reaction process) and must give a tetrapropionate adduct **109** that is easily manipulated to an aldehyde ready for the second coupling.

Within the scope of this research, it is desirable to synthesize nonracemic fragments as compounds isolated from nature are usually enantiopure. Coupling of nonracemic fragments is one of the ways of preparing complex enantiopure compounds. Using an enantiopure and stable derivative of aldehyde **110** should give access to enantiopure tetra and hexapropionate units via the first and third route. Thus, the synthesis of an enantiomerically pure aldehyde derivative of **110** was a part objective of this study. Enantiopure tetrapropionate fragment **109** would also result from an enantiotopic group selective aldol reaction of dialdehyde **115** with **112** in the presence of a suitable chiral mediator (Figure 17). A third objective of this research was to develop conditions to carry out such a process.

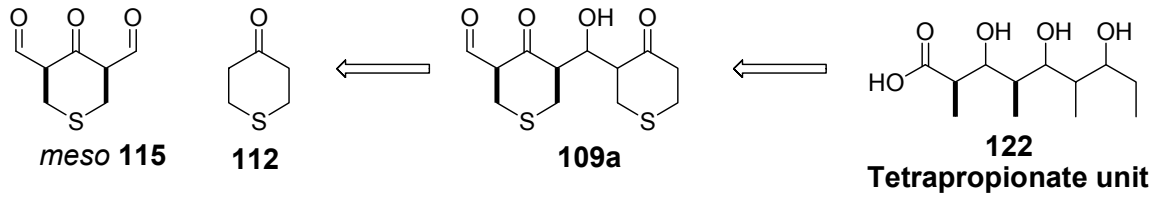
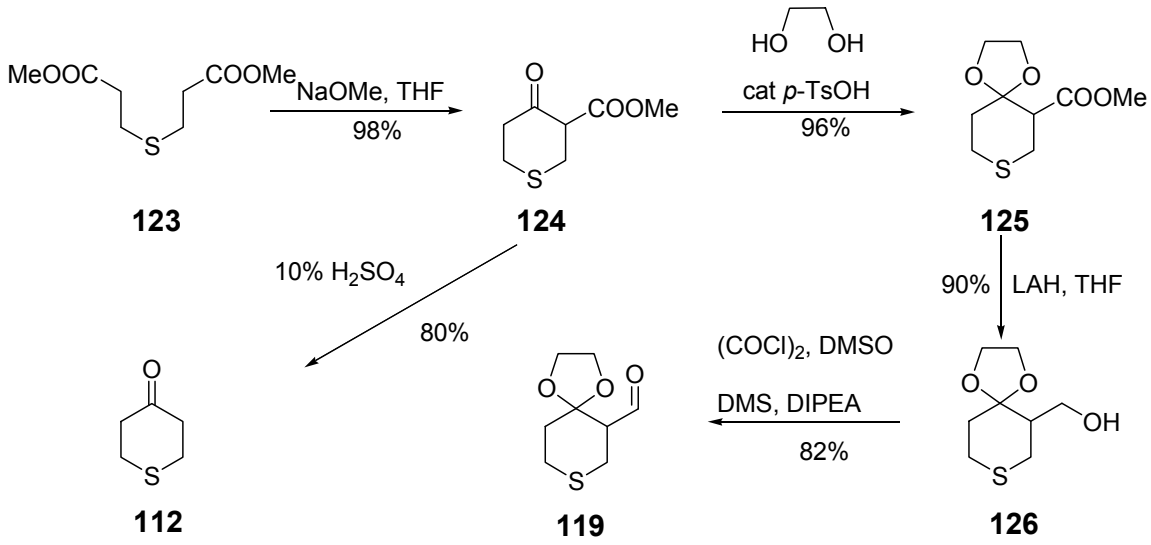


Figure 17: Retrosynthetic analysis on tetrapropionate unit via enantiotopic group selective aldol reaction

To get to enantioenriched hexapropionate units, coupling of enriched tetrapropionate fragments with enriched aldehyde derivate of **110** under conditions that would not generate *meso* compounds would afford enantiopure fragments. Equally, differentiating between the enantiotopic groups[124] in *meso* hexapropionate building blocks (generated via the different routes discussed above) using a chiral mediator should afford nonracemic fragments as well. This approach would be very desirable as it give access to chiral intermediates with six stereogenic centers in just a few steps from achiral starting materials.

From earlier work in the Ward group,[22] the ethylene ketal protected aldehyde **119** was shown to be an excellent substrate for stereoselective aldol reactions within route 1 in Figure 11. The aldehyde **119** was also selected for study within route 3, and it was prepared in 69% over 4 steps from commercially available materials using a method previously established in the group (Scheme 16).



Scheme 16: Preparation of the thiopyran aldehyde **119** and ketone **112**.

2.1.1 Summary of research objectives

The summary of my research objectives are listed below:

i) Identify and synthesize a practical thiopyran based *meso* dialdehyde **115**; ii) find conditions for a simultaneous two directional aldol reaction of the synthesized *meso* dialdehyde with ketone **112** to prepare *meso* hexapropionate synthons; iii) desymmetrize the *meso* hexapropionate synthon so prepared; iv) develop conditions for the desymmetrization of the enantiotopic groups in the synthesized *meso* dialdehyde; v) iterate the tetrapropionate unit so prepared in a second aldol coupling after appropriate functional group manipulations; vi) Identify and synthesize a suitable thiopyran based β–keto-carbonyl compound that can undergo a vinylogous aldol reaction with aldehyde **119**; vii) develop conditions for strereocontrolled aldol reactions of the synthesized β–keto-carbonyl compound with aldehyde **119**; viii) iterate an appropriate functionalized aldol adduct so prepared in a second aldol coupling; ix) develop a protocol for the preparation of enantiomerically pure **119.**

2.2 Synthesis of enantiopure 1,4-dioxa-8-thia-spiro[4.5]decane-6-carboxyaldehyde via enantioselective protonation.

2.2.1 Introduction

The concept of deracemization[125] by enantioselective protonation of a prostereogenic center under kinetic control to give a stereogenic one was first introduced by Duhamel in 1976. This topic has been studied extensively as evident in the hundreds of papers published over the last thirty years.[126-128] Duhamel in his 2004 review[126] listed about 19 different types of proton sources employed over the years to study this concept. One of the conditions that dictate the choice of chiral proton source (CPA) to be used in any study is the difference in the pK_a of the enol derivative to be protonated and that of the CPA. An optimum range of $2 \leq \Delta pK_a \leq 4$ has been suggested to be ideal for complete protonation by the CPA in order to obtain maximum ee[129,130]. Unfortunately pK_a values for most substrates to be studied are not known and as such structural similarities to literature examples play an important role in the choice of CPA to be used.

Inspired by the excellent result reported by Fehr[129,131] for the selective protonation of the enolates of 2,6,6-trimethyl-2-cyclohexene-1-carboxylic acid generated from its esters (Figure 18) using *N*-isopropyl ephedrine **130** (NIE) as the chiral proton source, and the similarity of that substrate to the substrates of choice for my study, the method was applied to various analogues of the thiopyran derived ketal ester. The results of the study are discussed in the following sections.

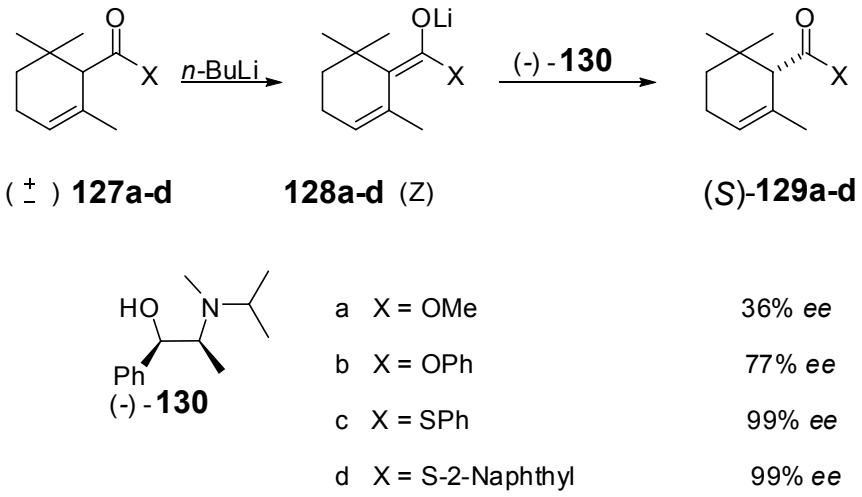
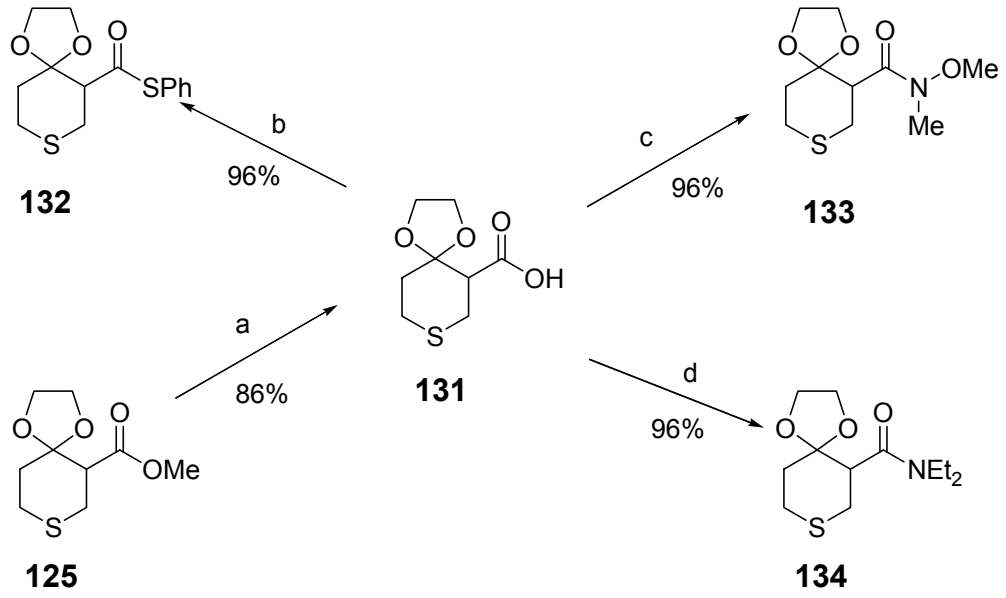


Figure 18: Enantioselective protonation of α-cyclogeranates and α-thiocyclogeranates

2.2.2 Preparation of thiopyran based analogues for enantioselective protonation study.

A number of racemic thiopyran based ester analogues were prepared for use as possible substrates for the enantioselective protonation study. The choice of substrate synthesized was dependent on its stability to the conditions for protonation and the anticipated relative ease of conversion to the final desired nonracemic aldehyde **119** with minimal loss of enantiomeric purity.

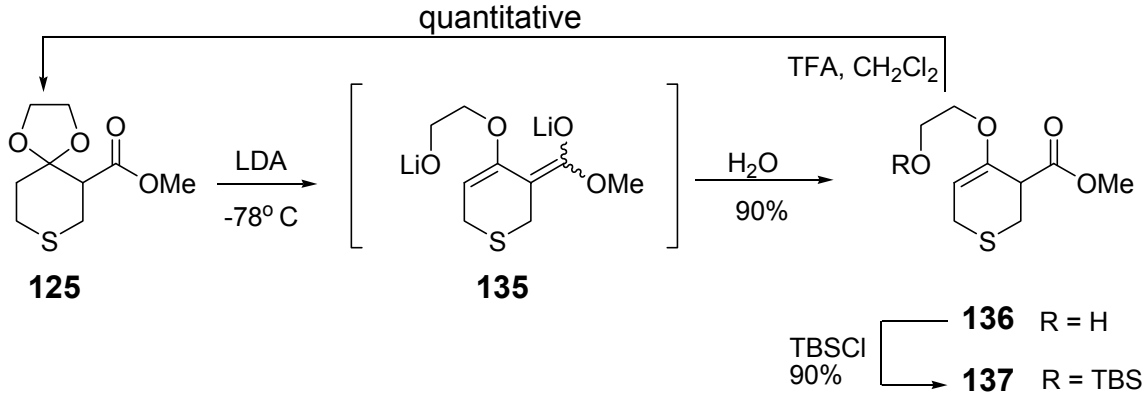


a) NaOH, H_2O, MeOH; b) I. $(COCl)_2$, II. HSPh, Et_3N; c) I. $(COCl)_2$, II. $HN(OCH_3)CH_3.HCl$, Et_3N; d) I. $(COCl)_2$, II. $HNEt_2$, Et_3N

Scheme 17: Preparation of thiopyran ester analogues.

Base hydrolysis of the ketal protected methyl ester **125** gave the acid **131** in good yield after re-crystallization (Scheme 17). Conversion of **131** to the acid chloride followed by reaction with the appropriate nucleophile in the presence of Et_3N afforded the various analogues **132-134** in good to excellent yields. As a prelude to the selective protonation study, the stability of **125**, **132**, **133** and **134** to the reaction conditions were tested. Formation of the respective lithium enolates at -78^o C using 1 equivalent LDA and subsequent quenching by addition of water afforded >95% recovery of starting material for only 2 out of the 4 analogues (**132** and **134**). Analysis of the products obtained from the deprotonation of **125** showed that the enolate generated at -78 ^{o}C was not stable and underwent elimination followed by a second deprotonation to give the alkoxide dienolate dianion **135** that on quench with water afforded compound **136** in 35% yield (Scheme 18). The use of excess of LDA[132] afforded **136** in 90% yield. Compound **136** was protected as its TBDMS ether derivative **137** that was equally considered as a candidate for the enantioselective protonation

study. Exposure of **136** to acid readily converts it back to **125** in quantitative yield.

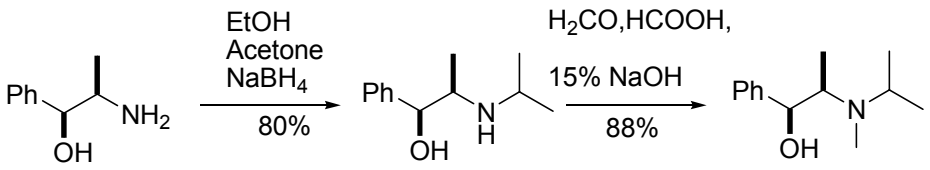


Scheme 18: Generation of the lithium enolate of **125**

Attempts to generate the lithium enolate of **133** did not meet with any success as the NMR spectrum of the crude reaction mixture after work up was very messy suggesting decomposition of the compound under the conditions for the enolate generation. Compound **133** was thus eliminated from further study.

To ascertain the degree of conversion to enolates under the reaction conditions, the enolates were quenched with a deuterium source (D_2O or CD_3OD) and the percentage deuterium incorporation at the α–position to the carbonyl group was determined by ^1H NMR (high deuterium incorporations were obtained in the reactions of **132** and **137**). In the case of compound **134**, the percentage incorporation was not quantifiable using the technique available, as such **134** was not considered for the study.

The chiral proton source **130** was prepared in 70% yield in two steps as shown in Scheme 19. Condensation of commercially available norephedrine with acetone in absolute ethanol furnishes an oxazolidine intermediate that was reduced with $NaBH_4$ to give the isopropyl derivative **139**. Eschweiler-Clarke alkylation[133] of the secondary amine gave the desired **130** after distillation that was homogenous by TLC and NMR and had a specific rotation commensurate with literature values.[129,131]



138 **139** (+)-**130**

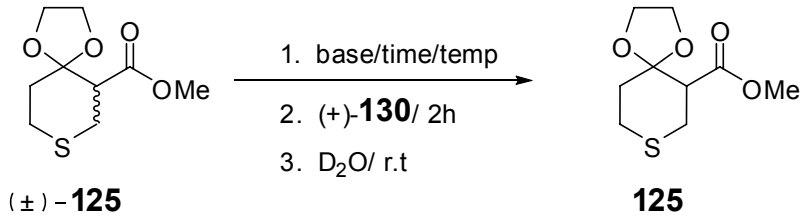
Scheme 19: Preparation of chiral proton source **130**.

2.2.3 Enantioselective protonation of thiopyran-3-carboxylic acid ester enolates.

2.2.3.1 Protonation of methyl 1,4-dioxa-8-thia-spiro[4.5]decane-6-carboxylate (110) and the TBDMS ether derivative (122)

Table 4 gives an overview of the results of the asymmetric protonation of the methyl ester derivatives **125** and **136** with **130**. Enolates were generated by adding a solution of the ester to the freshly generated base at the indicated temperature.

Table 4: Enantioselective protonation of enolates from **125** and **136** with (+)-**130**.



(±)-**125** **125**

Entry	ester	equiv **130**	base (equiv)	temp* °C	%ee**	%yield
1	**125**	5	LDA (3)	-78	5[a]	90[b]
2	**125**	5	*s*-BuLi (2)	-100	20	95
3	**137**	10	LDA (2)	-78	9	>90
4	**137**	10	LDA[c] (2)	-78	5	85
5	**137**	10	LDA (2)/ *n*-BuLi (2)[d]	-78	33	>90
6	**137**	10	LDA (2)/ *n*-BuLi (2)[d,e]	-78	60	>90
7	**137**	10	LDA (2)/ *n*-BuLi (2)[d,e]	-96	56	>90
8	**137**	10	*s*-BuLi (2)[f]	-78	20	>90

a) ee measured on **125** obtained from cyclization of **136**; b) 0.5 equiv TFA in CH_2Cl_2 for 30 min to close the ketal ring of **136** back to **125**; c) LDA, 2 h; d) LDA 30 min followed by *n*-BuLi for another 30 min; e) The pre-cooled proton source was added dropwise over 2 h; f) *s*-BuLi, 1 h

Note:>95% proton incorporation from **130** was obtained in all experiments.

* Temperature for formation and quench of enolate (bath).

** Determined by ^{1}H NMR in the presence of (S)-(+)-2,2,2-trifluoro-1-(9-anthryl) ethanol as chiral solvating agent (1.5 equivalent, in 0.05M concentration).

Quenching the enolate of **125** generated with excess LDA (3 equiv) at -78 ^{o}C with 5 equiv of (+)-**130** returned **125** in very low ee (5%) after subjecting the product **136** from the reaction to acid catalyzed cyclization. The use of *s*-BuLi (2 equiv) as base at -100 ^{o}C gave a stable enolate which afforded **125** in 20% ee on quench with (+)-**130** at the same temperature. This result is not surprising and fits within the range reported by Fehr (36% ee)[129] for the O-methyl ester **127a** (Figure 18). The low ee was attributed to the relatively small structural differentiation between the enolate substituents (OLi vs OMe) in the interaction with the chiral proton source.

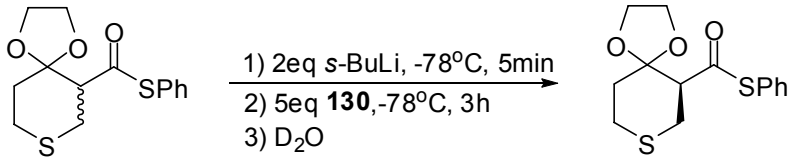
Quenching the lithium enolate of **137** generated from reaction with LDA (2 equiv.) at -78 ^{o}C gave a similar low ee (9%) (entry 3). Increasing the reaction time for the enolate generation did not improve the ee (5%) suggesting that the conditions for enolate generation were not appropriate. In the course of validating the conditions for complete generation and protonation of the enolate from **137**, it was observed that only 70% deuterium incorporation was obtained on quenching the enolate with D_2O or CD_3OD. Addition of 2 extra equivalents of *n*-BuLi prior to quenching gave complete deuteration suggesting the possibility of 'internal proton return'[134], a phenomenon that might also account for the low ee observed. Applying this protocol gave a slightly higher ratio of enantiomers 2:1 (33% ee entry 5). Encouraged by this slight improvement in selectivity of the protonation, the temperature of the chiral proton source on addition was investigated. Addition of room temperature **130** into a solution of enolate at -78 ^{o}C will increase the local temperature of the reaction mixture and if the protonation is fast, then the temperature during quench will be higher than -78 ^{o}C. To adjust for this hypothesis, the chiral proton source was pre-cooled prior to addition and was added slowly over 2 h. Interestingly the enantiomer ratio of the product **137** increased to 4:1 (60% ee entry 6) under these conditons. Further lowering the reaction temperature did not improve the selectivity (entry 7). Generating the lithium enolate under amine free condition (2 equiv. *s*-BuLi) gave a poorer result (entry 8).

Although the ee obtained from enantioselective protonation of the enolate from **137** was much higher than that obtained from **125**, the selectivity was still impractically low and could not be improved any further.

2.2.3.2 Protonation of (*S*)-Phenyl 1,4-dioxa-8-thia-spiro[4.5]decane-6-carbothioate (132).

Optimal conditions for the generation and quenching of the lithium enolate from **132** were established as follows: addition over 1 min of 2 equiv. of *s*-BuLi at –78 ^{o}C and, after 5 mins, slow addition of **130** over 2 h followed by the addition of D_2O after an additional 1 h to verify complete protonation of enolate by the chiral proton source. The results of the optimization study are summarized in Table 5.

Table 5: Enantioselective protonation of the Li enolate of **132** with **125**



(±)-**132** (−)-**132**

Entry	Mmol **132**	Addition time(h)	Mmol **130**	conc [M] **130**	conc [M] **132**	% ee
1	0.07	2	0.43	0.21	0.02	71
2	0.07	2	0.35	0.16	0.01	75
3	0.07	2	0.35	0.09	0.005	20
4	0.07	3.5	2.60	0.26	0.05	60
5	0.07	4.5	5.78	0.58	0.08	50
6	0.07	5	23.64	0.59	0.06	64

Note: % ee was measured by ^{1}H NMR of the Mosher's ester of the alcohol obtained by $LiAlH_4$ reduction . Yields from selective protonation were >95% in all cases.

The results of these studies only gave moderate enantioselectivity with the best ratio of 7:1. This was a slight improvement compared with the best result observed for the methyl ester **137** (4:1), but not comparable to the result obtained by Fehr[129] for the S-phenyl ester of a structurally similar compound (>50:1, >98% ee). On scaling up the reaction under the conditions used in entry 1, the selectivity decreased. Initially, the selectivity observed from multiple experiments under same reaction condition as entry 1 but with a slight variation in concentration suggested a dependence on the total concentration of the reaction mixture. The more dilute the reaction mixture, the higher the selectivity. To investigate this hypothesis, the reaction was carried out at 0.01M and 0.005M (a dilution factor of 2 and 4) total concentration. The observed selectivity at 0.01M (entry 2) was slightly improved to 75% ee (7:1 er); however, the selectivity obtained at 0.005M was much lower 20% ee (1.5:1 er). These results suggest that an optimum concentration/ selectivity combination hovers around 0.01M giving a 7:1 ratio of enantiomers. This study further suggests that the total concentration of the reaction mixture is not the only factor responsible for the varying selectivity observed in the reaction.

In the study of protonation of the enolates from methyl ester **125** and **137**, it was established that the rate of addition of the chiral proton source greatly affects the observed selectivity (for **137**, 33% ee to 60% ee for addition over 2 mins and 2 h, respectively). This result suggested that selective protonation may occur from a complex species whose formation will be dependent on concentration of the reaction mixture. To test this notion, 1 equivalent of the lithium alkoxide of **130** was added to the enolate from **132** prior to addition of **130** at a fast rate. The result obtained (50% ee (3:1 er) did not support the proposed complex formation.

To test the effect of temperature on the selectivity of the protonation, the enolate from **132** was generated at -100 ^{o}C and quench with the chiral proton source at the same temperature. This experiment revealed that the rate of protonation is very slow at this temperature (< 5% protonation over after 1 h). As a control experiment to determine if racemization occurs during the reaction, an

enriched sample was subjected to the reaction condition (lithium alkoxide of **130**) and the ee was monitored over time. Approximately 5% racemization per hour was observed under these reaction conditions. The fact that **132** is not configurationally stable to the reaction condition might account for the variations observed in the ee of the products.

The reaction procedure was modified to optimize the selectivity of the protonation based on the information obtained from the above control experiments. The CPA (-)-**130** was added at once to the lithium enolate of **132** generated from *s*-BuLi at -78 ^{o}C and cooled to -100 ^{o}C. The mixture was then allowed to warm to -78 ^{o}C over 40 mins and kept at that temperature for another 2 h. Addition of water followed by acidic workup to remove the proton source returned **132** in 82% ee (10:1 er). This process gave reproducible results and was amenable to scale up (gram scale).

Although the selectivity achieved from the study is modest and far lower than that obtained by Fehr[129], this procedure still constitutes a very useful method owing to the fact that **132** is crystalline. Enriched (-)-**132** (10:1 er) is obtained from the enantioselective protonation reaction in high yield (>95%) (Figure 19). More importantly, the enriched **132** can be purified to >95% ee (50% yield) by recrystallization (>98% ee obtained by 3 recrystallization). The process is efficient because the product recovered from the mother liquors can be resubjected to the enantioselective protonation.

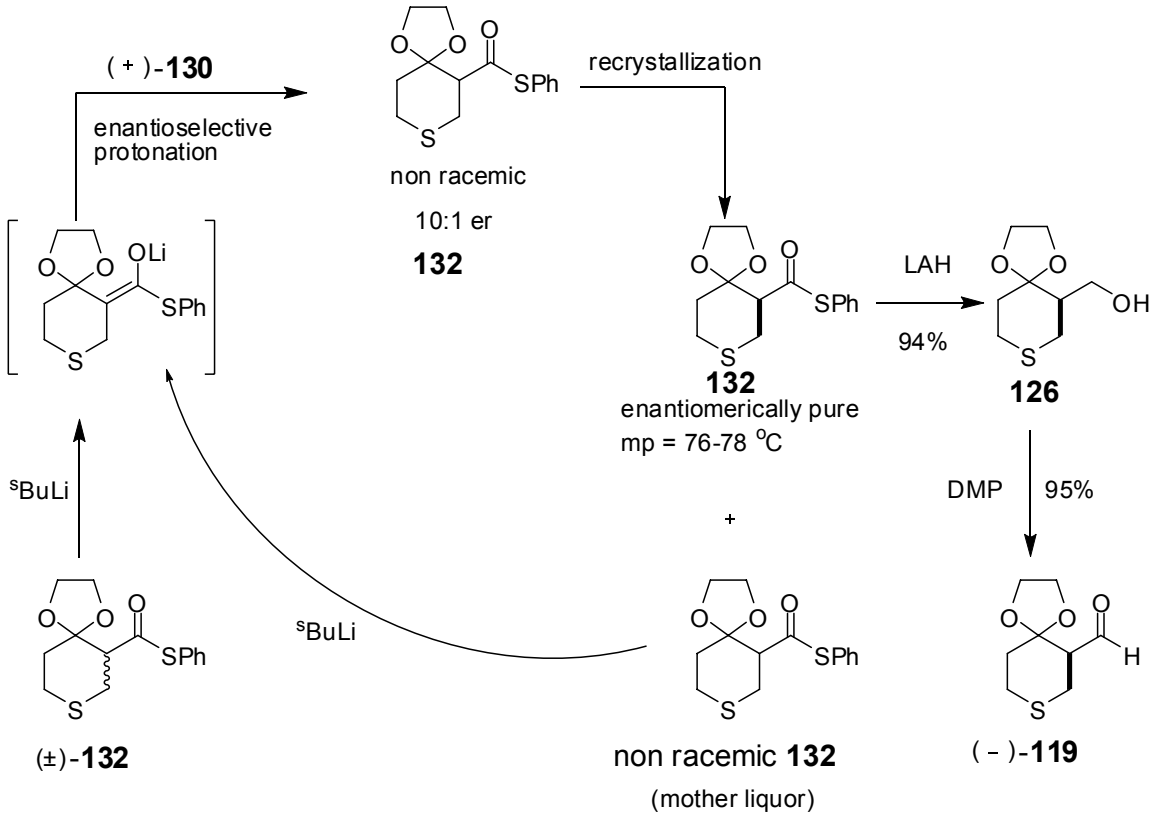


Figure 19: Preparation of optically pure aldehyde **119**

Reduction of the enantiopure thioester **132** with $LiAlH_4$ afforded the alcohol **126** without detectable racemization. The alcohol **126** was oxidized using the Dess-Martin[135] periodinane to give **119**. The efficacy of this oxidation protocol was previously established in the group by Idralyn Alarcon.[120]

Because the absolute configuration of **126** has been previously assigned, it is concluded that protonation of the Li enolate from **132** with (+)-**130** gives (*R*)-(-)-**132**, this configuration also conforms to what was observed by Fehr[129] for the protonation of **128** with **130** (Figure 18).

2.2.3.3 Summary and Conclusions

The preparation of the enantiopure aldehyde **119** was successfully achieved in > 95% ee and 50% yield from **132** via a combination of enantioselective protonation of the lithium enolate of **132** generated from its reaction with *s*-BuLi and recrystallization. Reduction of the enantioenriched **132** followed by oxidation furnished the desired aldehyde **119**. Although the ee obtained from the protonation reaction is modest, this process still constitutes an efficient way to obtain the aldehyde as the chiral proton source can be recovered and reused. The material recovered from the mother liquor is equally reusable without any purification (see Figure 19).

2.3 Design, synthesis and aldol reactions of β-ketocarbonyl analogues of thiopyranone.

2.3.1 Introduction.

The choice of the β–ketocarbonyl analogues of thiopyranone to be synthesized and used for the study of the proposed route 3 (Figure 4) is dependent on two factors. The first is that dienolate (or equivalent) derivatives of the analogue must preferentially undergo addition to the γ–position rather than the α–position and secondly the carbonyl group (or synthetic equivalent) should be readily converted into an aldehyde group for further couplings. Silyl dienol ethers derived from β–keto esters and 1,3-dioxin-4-one derived dienolates have been successfully[123] used in vinylogous aldol reactions under Mukaiyama[114] conditions. It follows that dienol derivatives of thiopyranone β–ketoesters or β–ketoaldehyde (e.g. **135**) might be ideal candidates that fulfill the required conditions (Figure 20). Attempts at synthesizing these types of analogues and evaluation of several in the proposed 3rd route in Figure 11 are discussed in the following sections. The ultimate objective of this route is to use the previously described enantiopure aldehyde **119** (section 2.2.3.2) for the vinylogous aldol reaction with **135** to furnish enantiopure tetrapropionate synthons that might be used directly in natural product synthesis or be transformed into higher oligomers by an iterative process.

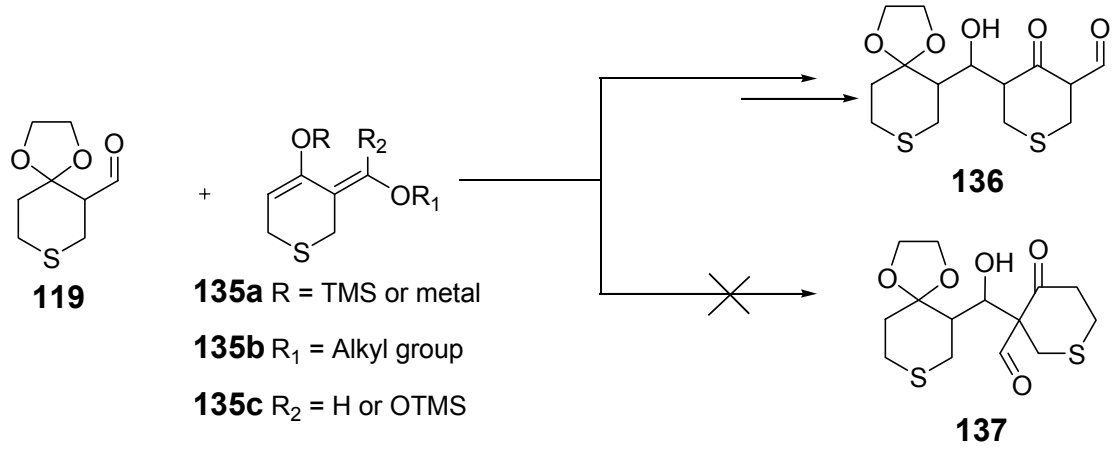
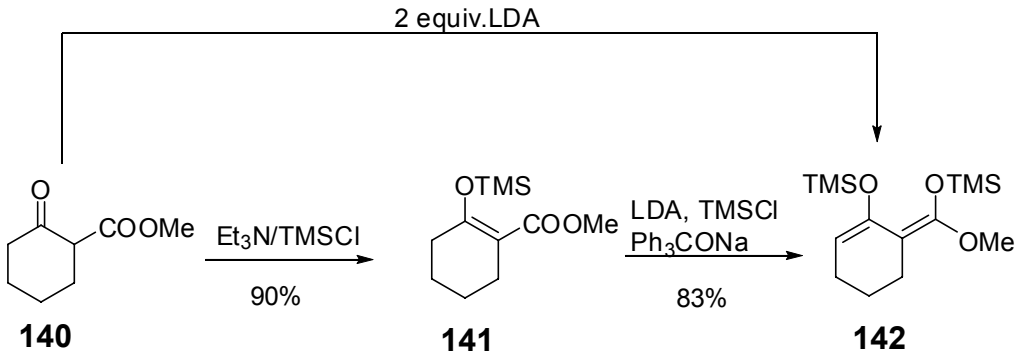


Figure 20: Vinylogous aldol reaction.

2.3.2 Synthesis of dienolate derivatives of thiopyranone β-ketocarbonyls.

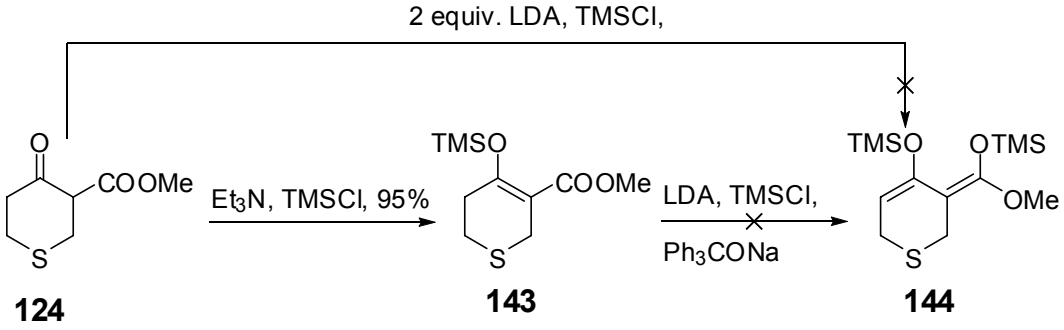
2.3.2.1 Attempted synthesis of a 1,3-bis(trimethylsiloxyl)-1,3-diene analogue.

Langer and Schinder[136] published procedures for the preparation of 1,3-bis(trimethylsiloxyl)-1,3-dienes from six membered cyclic β-ketoesters (Scheme 20). The best procedure involves the generation of the thermodynamically favoured silyl enol ether using TMSCl and Et_3N followed by reaction of the product with LDA and trapping the resulting enolate with TMSCl to afford the desired product. A more direct approach simply involves the use of 2 equivalents of LDA (or other strong base) and then trapping the resulting dilithium dienolate with TMSCl.



Scheme 20: Langer's synthesis of a cyclic 1,3-bis (trimethyl siloxyl)-1,3-diene.

Application of the Langer procedures to the synthesis of **144** failed (Scheme 21). Isolation of the desired product from the crude reaction mixture was never achieved as the compound readily decomposes even at 0 ^{o}C. The addition of sodium triphenylmethoxide to stabilize the product, as reported by Krageloh and Simchen,[137] was not effective in preventing polymerization. Because pure samples of **144** could not be obtained, this compound was not investigated further.



Scheme 21: Attempted synthesis of 1, 3-bis (trimethylsiloxyl)-1,3-diene analogue of thiopyranone.

2.3.2.2 Attempted synthesis of a dioxine analogue.

Sato *et al.*[138,139] provided the first example of the use of dioxins[138] in enantioselective vinylogous aldol reactions. Dioxine **146** has been employed in a

number[123] of enantioselective total syntheses with good results (Figure 21). The aldol products obtained from reaction with **146** can be easily transformed to β–ketoesters via alcohol mediated hydrolysis of the acetal and the ester group can be readily converted to an aldehyde group for further aldol couplings.

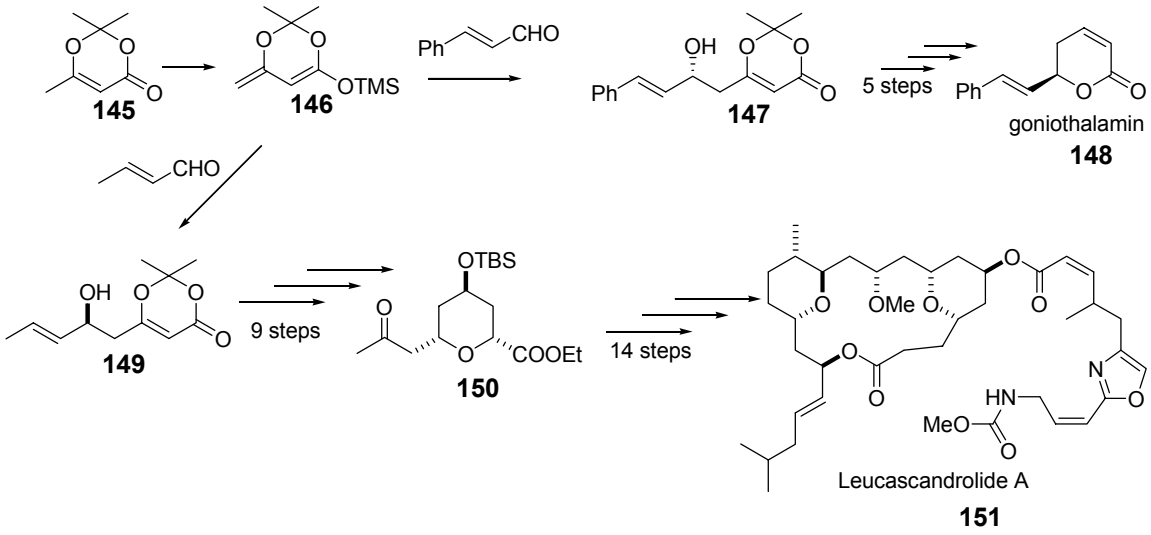
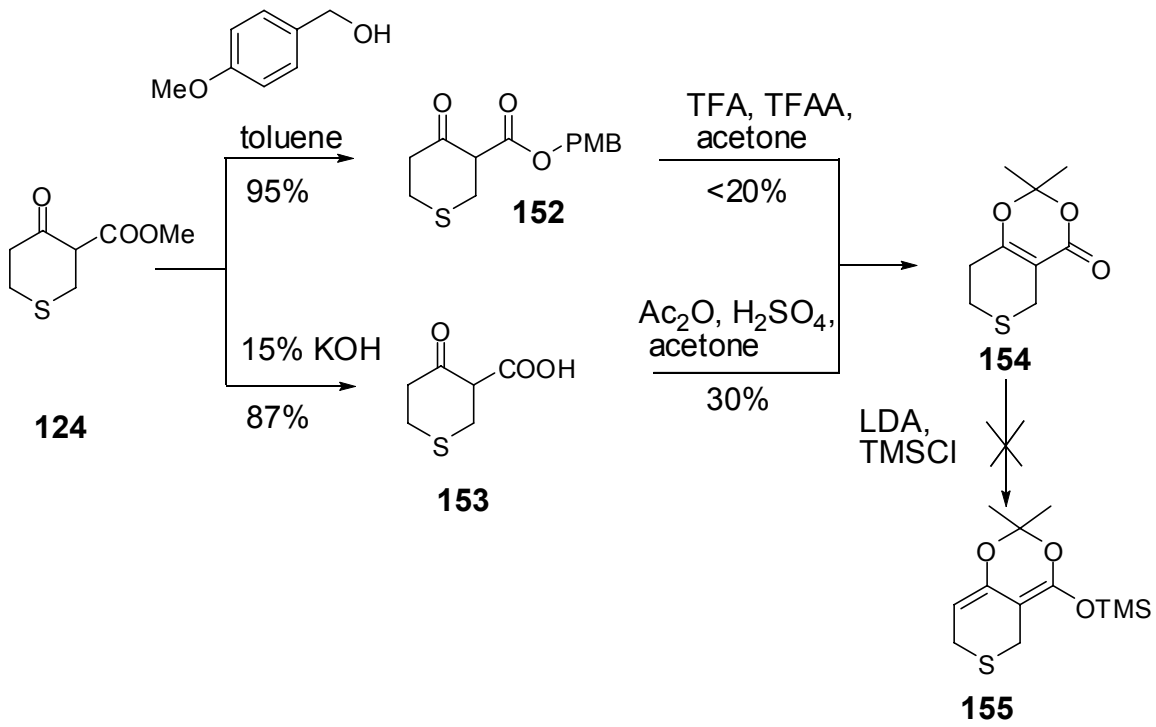


Figure 21: Examples of the use of dioxines in natural products synthesis.[139,140]

The two approaches reported for the synthesis of dioxinones from acyclic starting materials were investigated for synthesis of the dioxinone analogue of thiopyranone, **155** (Scheme 22).



Scheme 22: Attempted synthesis of the dioxine 1,3-diene analogue.

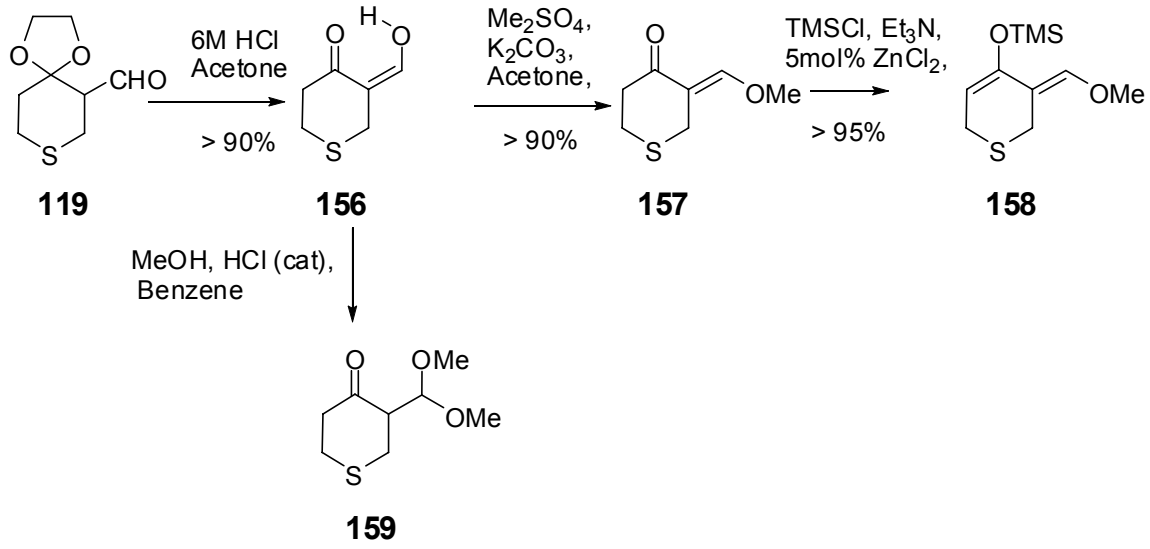
Transesterification of **124** with *p*-methyl benzyl alcohol in refluxing toluene gave ester **152** in excellent yield. Transformation of **152** to the dioxinone using TFA and TFAA afforded an inseparable mixture of products that included the dioxinone **154** in < 20%[†] yield. An alternative approach via the acid **133** using acetic anhydride and catalytic sulphuric acid gave the desired dioxinone **154,** albeit in low yield (30%). Attempts to transform **154** to the desired **155** failed as the product could not be isolated due to rapid polymerization. This problem ultimately led to abandoning **155** as a possible substrate for the vinylogous aldol reaction.

[†]Estimated from the ^{1}H NMR spectrum of the crude mixture.

2.3.2.3 Synthesis of the methoxymethylidene derivative of thiopyranone (158).

The most direct method for the preparation of **158** involves the formylation of thiopyranone, followed by the protection of the resulting β-ketoaldehyde **156** with a group that would be stable under aldol reaction conditions but could be easily removed to give the aldehyde without retroaldol. Attempts to reproduce the formylation procedure reported for the preparation of **156** by Anisworth[141] and Berlin[142] failed. Their method involves the use of NaOMe and ethyl formate in benzene at room temperature overnight affording 30% of the desired product. Despite varying the reaction conditions (reaction time, solvent and temperature) the desired compound was never detected formed in any appreciable amount. Synthesis of the methoxymethylidene compound **158** was eventually accomplished via an indirect method (Scheme 23). Hydrolysis of the ketal group in racemic aldehyde **119** under acidic conditions afforded the β-ketoaldehyde enol **156** in good yield. Attempts to form the methyl enol ether **157** from **156** under acidic condition only yielded the dimethyl acetal **159**. Alkylation of **156** with Me_2SO_4 under basic conditions gave the desired O-alkylated compound **157** in yields > 90%. Compound **157** was readily transformed to **158** by reaction with TMSCl, Et_3N and a catalytic amount of $ZnCl_2$[143] in very good yield. The transformation of **157** to **158** was not achievable in the absence $ZnCl_2$.

It is noteworthy that compounds **156**, **157** and **158** are highly reactive and easily decompose at room temperature within minutes when neat and in less than 2 days at –20 ^{o}C. As such, they were freshly prepared and used as needed.



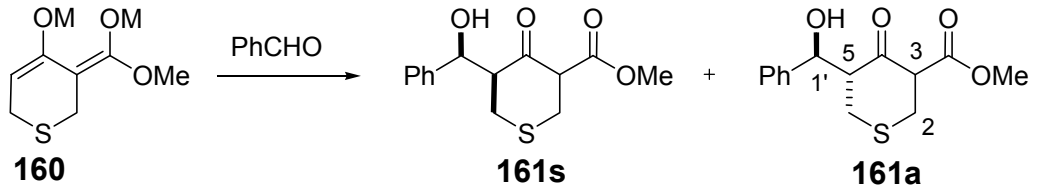
Scheme 23: Synthesis of the methoxymethylidene analogue.

2.3.3 Aldol reactions of dienolates generated from the β–ketoester 124.

The aldol reactions of the dienolate generated from β–ketoester **124** is presented in the following sections. The first describes a model study to determine the intrinsic selectivity of dienolates generated under various conditions from **124** in the aldol reactions with benzaldehyde. Benzaldehyde was selected for the model study so that the diastereoselectivity of the aldol reaction would be largely dependent on the dienolate and that the structures of the aldol products would also be relatively easy to determine. The second sub-section describes the reaction of the dienolates with the thiopyran aldehyde **119**.

2.3.3.1 Reaction of β–ketoester dienolates with benzaldehyde- A model study.

The dilithium dienolate of **124** was generated following two methods, one by reaction with LDA and the second under amine free conditions[21] using *s*-BuLi. The mixed Na/Li dienolate of **124** was generated according to Weiler's procedure[144] and the Ti(IV) dienolate was generated from the reaction of **124** with $TiCl_4$ and 2 equivalents of DIEA. The diastereoselectivities of the aldol reactions with benzaldehyde are shown in Table 6.



160 **161s** **161a**

Table 6: Aldol reaction of **160** with benzaldehyde

Entry	M(base, equiv)	**161s:161a**	combined % yield
1	Li (LDA, 3)	1 : 8	60-65
2	Li (*s*-BuLi, 2)	1 : 8	40
3	Na/Li(NaH/*n*-BuLi,1.2)	1 : 1.8	40
4	Ti ($TiCl_4$/DIEA, 2)	1 : 12	25

Addition of benzaldehyde to the dilithium dienolate generated by reaction of **124** with 3 equivalents of LDA gave a mixture of aldol products with a combined yield of 60-65%. A careful analysis of the ^1H NMR of the crude mixture after work up revealed a mixture of 6 products that can be separated into two groups in a 8:1 ratio. Each group constitutes an equilibrium mixture of the two possible β-ketoester diastereomers and the enol ester (Figure 22).

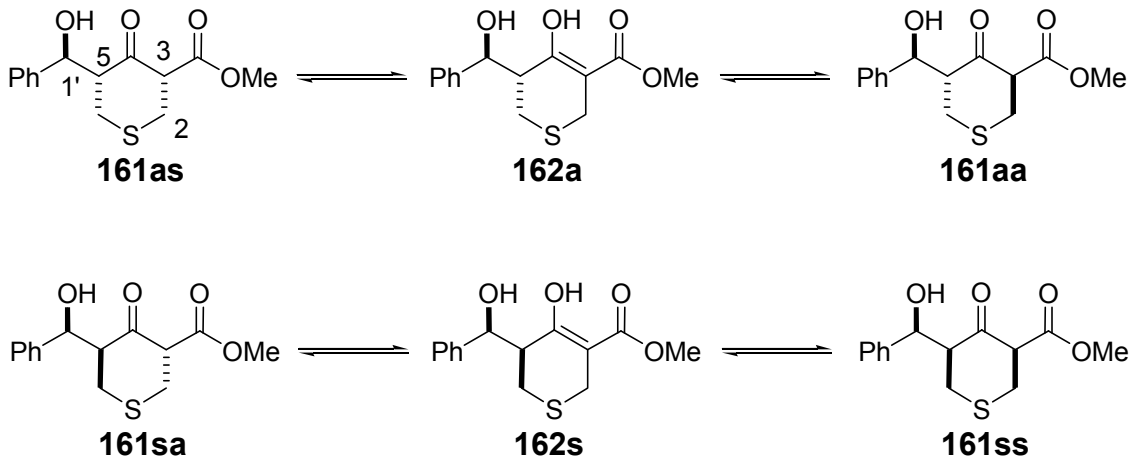


Figure 22: Equilibrium mixture of the aldol products.

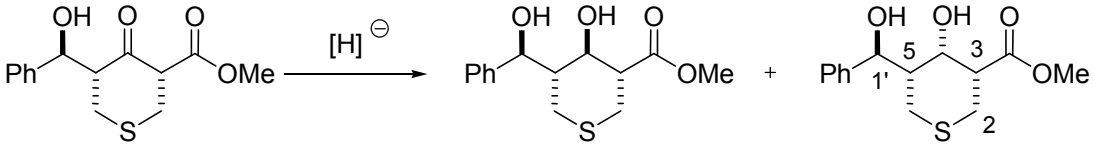
The compounds are grouped based on the size of the coupling constant between HC-5 and HC-1'. For the three *anti* diastereomers, $J_{5\text{-}1'}$ were 8, 8.5 and 8.5 Hz and for the three *syn* diastereomers, the values were found to be 2, 3 and 3.5.Hz. The two groups can be separated by flash column chromatograpy. Crystallization of the *anti* diastereomers [from a mixture of ethyl acetate:hexanes (1:4 v/v)] afforded a single crystalline compound in >50%. The diastereoselectivity of the aldol addition favored the *anti* isomer in all cases. The diastereoselectivities of the reactions of the dilithium dienolates generated with LDA and ^{s}BuLi were the same and higher than that for the Na/Li dienolate (Table 6, entry 3). The highest selectivity was obtained with the titanium dienolate but the yield was very low. Attempts to improve the yield by varying the reaction conditions (reaction time, stoichiometry, reaction concentration and temperature) gave no appreciable increase.

The crystalline *anti* aldol product **161as** was stereoselectively reduced[145] (Table 7) to afford the 1,3-*anti* diol **163ass** that was converted to the acetonide[146,147] allowing for unequivocal determination of the relative configurations to be 1',5-*anti*-3,5-*cis* [‡] . It is worth mentioning that the

[‡] See section 2.6.1.1 for a detailed discussion of the structure determination.

diastereoselectivity of the reduction of **161as** to the 1,3-*anti* diol adduct **163aaa** was higher when the reducing reagent was added as a solid compared to when it was generated *in-situ* (Table 7, entries 2 and 3). The 1,3-*syn* selective reduction[148,149] of the crystalline *anti* aldol adduct **161as** was carried out to afford the expected diol **163aaa** as the major product in 11:1 ratio (Table 7, entry 5). The determination of the relative configuration of the aldol product **161as** is discussed in detail in section 2.6.

Table 7: 1,3- selective reduction of **161as**



161as **163aaa** **163ass**

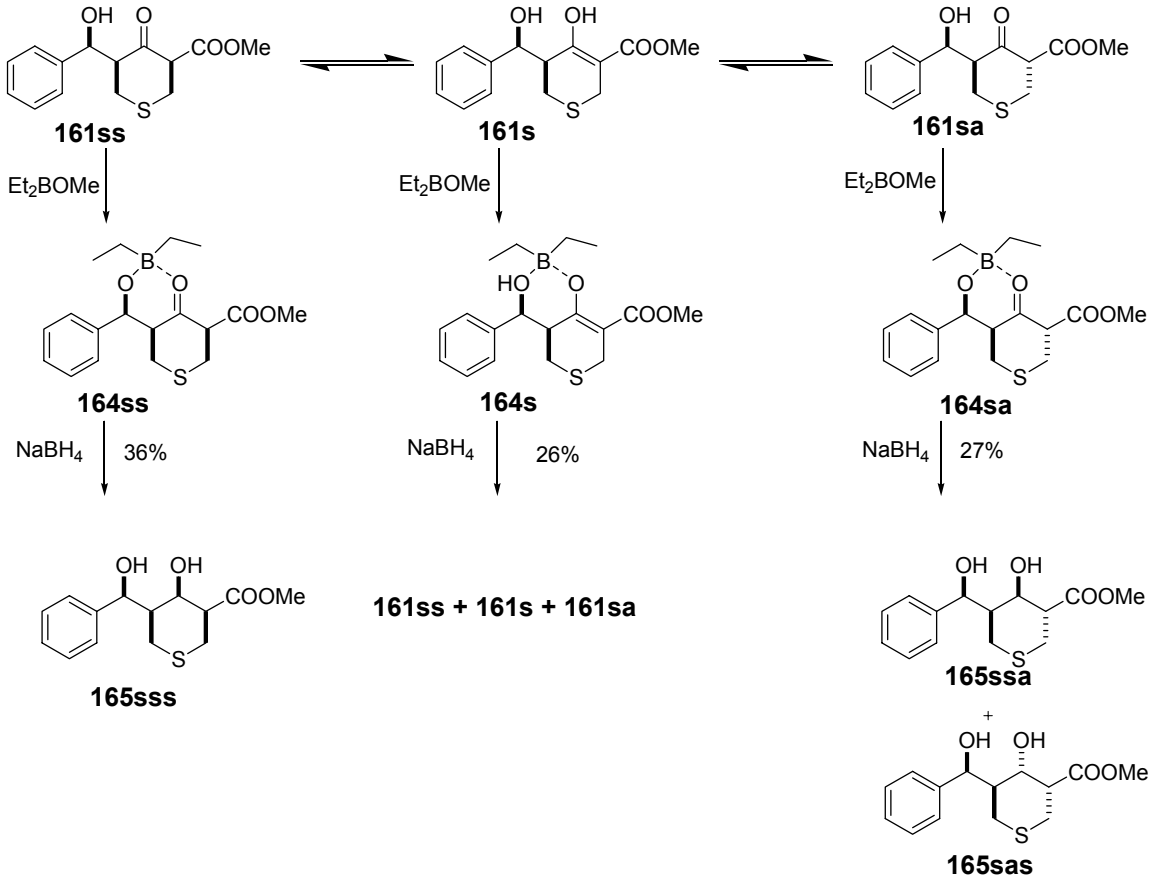
Entry	substrate	condition	**163aaa:163ass**	combined% yield
1	**161as**	$NaBH_4$	1 : 1	55
2	**161as**	$NaBH(OAc)_3$[a]	1 : 20	80
3	**161as**	$NaBH(OAc)_3$[b]	1 : >50	93
4	**161***	$NaBH(OAc)_3$[a]	1 : 10	73
5	**161as**	$NaBH_4$/ Et_2BOMe	11 : 1	80

a) generated *in-situ*, 0 ^oC; b) added as a powder, 0 ^oC

* Equilibrium mixture of the keto and enol forms of *anti* aldol adduct **161a**

$NaBH(OAc)_3$[145] reduction of the keto-enol mixture of *syn* aldol adducts **161ss** gave a 1:1.6 ratio of inseparable diol adducts. The structures of these diol adducts were not assigned. Attempts to carry out a 1,3-*syn* selective reduction of **161ss** using $NaBH_4$/ Et_2BOMe[148,149] gave a mixture of three diol products together with starting materials (Scheme 24). The reaction could not be driven to

full conversion presumably as a result of the formation of the enol borinate **164s** that is stable to reduction but on workup reverts back to the starting material.

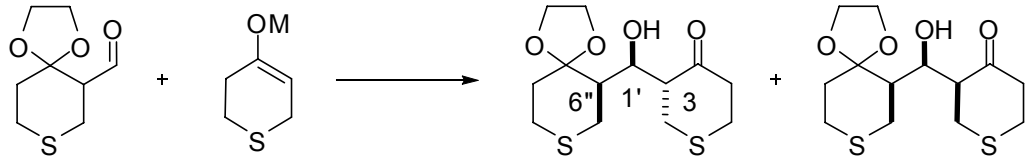


Scheme 24: 1,3-*syn* selective reduction of the mixed *syn* aldol adducts

Fractionation of the reaction mixture gave the all *syn* diol adduct **165sss** in 36% yield. The structure of **165sss** was assigned based on the small coupling constants in HC-4 (brs) that is most easily rationalized assuming an axial hydroxyl group with the two other substituents in the equatorial orientation. In addition, a 7:1 ratio of inseparable diol were isolated in 27% combined yield. These diol adducts were presumably **165ssa** and **165sas** but the structures were not assigned unambiguously.

2.3.3.2 Reaction of dilithium dienolate of β–ketoester of 124 with thiopyran aldehyde 119.

Aldol reactions of dienolates of β–ketoester of **124** with the ketal protected aldehyde **119** can potentially give four diastereoisomeric products **166** if the labile configuration at HC-3 is not considered (Figure 24). Previous work in the Ward group[20-22] has shown that addition of the lithium enolate **118** (M = Li) to aldehyde **119** occurs with 'Felkin' diastereoselectivity (i.e. to give the 1',6''-*syn* product) and *anti* topicity to give **120as** with good selectivity (Figure 23).



119 **118** (M = Li) **120as** : **120ss**

9 : 1

Figure 23: Reaction of lithium enolate **118** to ketal aldehyde **119**

The aldol reaction of dilithium dienolate **160a** with benzaldehyde gave *anti* simple diastereoselectivity comparable to that observed for the reaction of thiopyranone lithium enolate **118** (see Section 2.3.3.1).

With these results in mind, aldehyde **119** was added to the dilithium dienolate **160a** generated from **124** by reaction with LDA to furnish a mixture of aldol products in 72% yield (Figure 24). A careful analysis of the ^{1}H NMR of the crude mixture revealed that all the four possible diastereoisomers from the reaction were present (4 possible diastereoisomers if the labile configuration at HC-3 is not considered). This conclusion was supported by the observation of four distinct enol signals in a 1.5:1:3.3:5 ratio at δ 12.70, 12.86, 12.98 and 13.04, respectively. A solution of the crude aldol product in ethyl acetate and hexane gave a precipitate (33%) on standing for several days. The solid was shown to be **168as** (on standing in $CDCl_3$ for > 5 days, the ^{1}H NMR spectrum of **168as**

showed an enol proton at δ 12.86 ppm). The determination of the relative configuration of the aldol adduct **168as** is discussed in section 2.6. Due to the difficulty encountered in isolation and characterization of the products obtained from this reaction, β-keto ester compound **124** was no longer considered as a practical substrate to study the proposed route 1 (Figure 11).

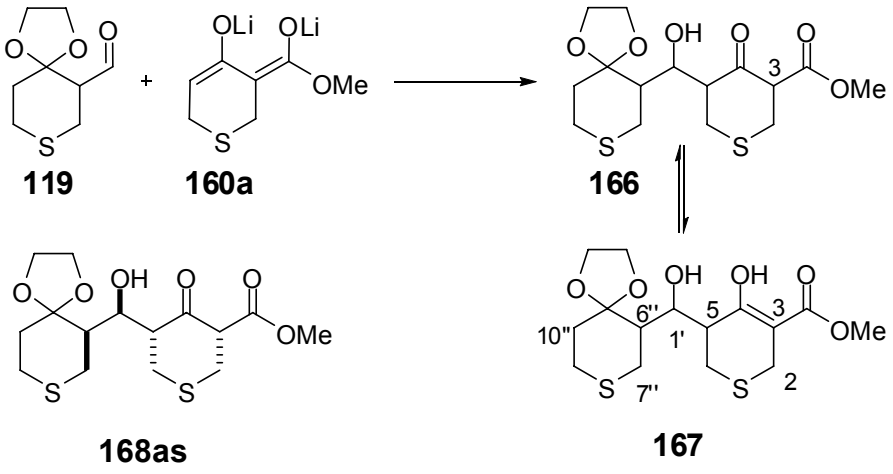
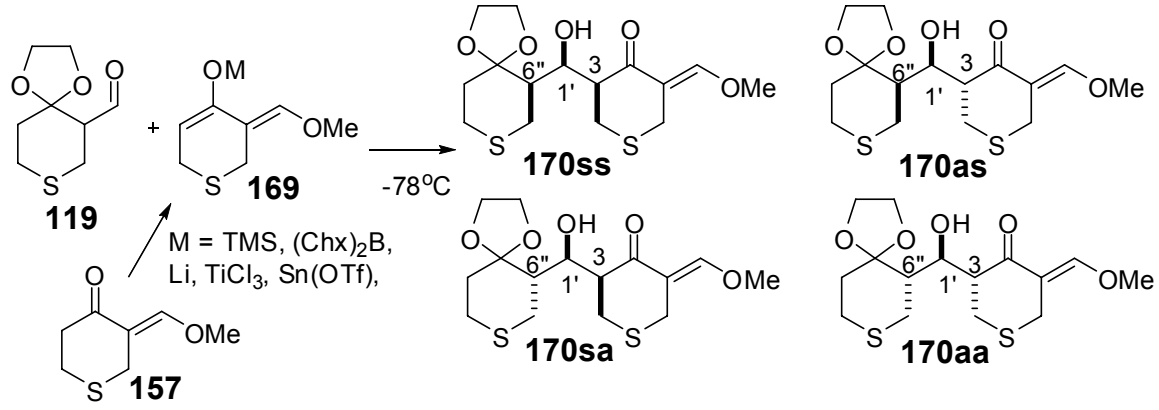


Figure 24: Aldol reaction of β–ketoester dienolate **160a** with **119**

2.3.4 Aldol reactions of tetrahydro-3-(methoxymethylidene)thiopyran-4-one (157)

The aldol reaction of **157** with racemic aldehyde **119** under various conditions was investigated. The reaction can potentially give four diastereomeric products (Table 8). One aim of this study was to find conditions that would preferentially afford one out of the four diastereomeric products selectively as this would give access to tetrapropionate fragments in one carbon forming reaction.

Table 8: Summary of aldol reactions of **119** and **169**



Entry[a]	M	Lewis acid	ss : as : aa : sa	yield%
1	$SiMe_3$	$TiCl_4$	5.6: 1 : 3.5 : -	76
2	$SiMe_3$	$SnCl_4$[b]	15 : 1 : - : -	50
3	$SiMe_3$	BF_3▪OEt_2	3 : 2 : 1 : -	32
4	$SiMe_3$	$MgBr_2$ ▪OEt_2[c]	- : - : 1 : 1.5	85-95[d]
5	$SiMe_3$	Me_2AlCl	- : - : 1 : 1.5	40
6	$TiCl_3$[e]	-	5-9 : 1 : - : -	76
7	Sn(OTf)	-	1 :trace: - : -	50
8	$(Chx)_2B$[f,g]	-	1 : 12: - : -	78
9	Li (LDA)	-	1 : 1 : 1 : -	35
10	Li (amine free)[h]	-	3.5 : 3 : 1 : -	60

a) All reactions conducted at -78 °C; b) $SnCl_4$ added as a solution in DCM; c) reaction was conducted at 0 °C; d) yield in range due to varying amount of suspected elimination product; e) (-)-spartiene was used as base for enolate generation; f) Et_3N was used as base for enolate generation; g); enolate generated at -40°C h); enolate generated by adding 0.95 equiv. MeLi to **158** in THF at rt for 1 h.

Mukaiyama[114] type aldol reactions of **158** with **119** mediated with various Lewis acids were investigated. The reactions mediated by $TiCl_4$ and BF_3▪OEt_2 (Table 8 entries 1 and 3) gave 3 out of the 4 possible products with low

stereoselectivity. In both cases, the 1',3-*syn*-1',6''-*syn* [§] product **170ss** was predominant. Under the same conditions, the reaction of **117** with **119** gave much better diastereoselectivity (Table 9 entries 1 and 3)[22] favouring the 1',3-*syn*-1',6''-*syn* product **120ss**. The *syn*-selective aldol topicity obtained for the $TiCl_4$ and BF_3▪OEt_2 mediated reaction of **117** with **119** was rationalized based on an 'open' transitions state model in which both steric and electronic interactions (dipole-dipole interactions between the oxygen of the silyl enol ether and aldehyde) favour the transition state leading to the observed product (Figure 25).[150] Invoking the same model accounts for why the 1',3-*syn*-1',6''-*syn* product **120ss** is the major adduct from the reaction of **169** (M = TMS) with **119** promoted by $TiCl_4$ and BF_3▪OEt_2.

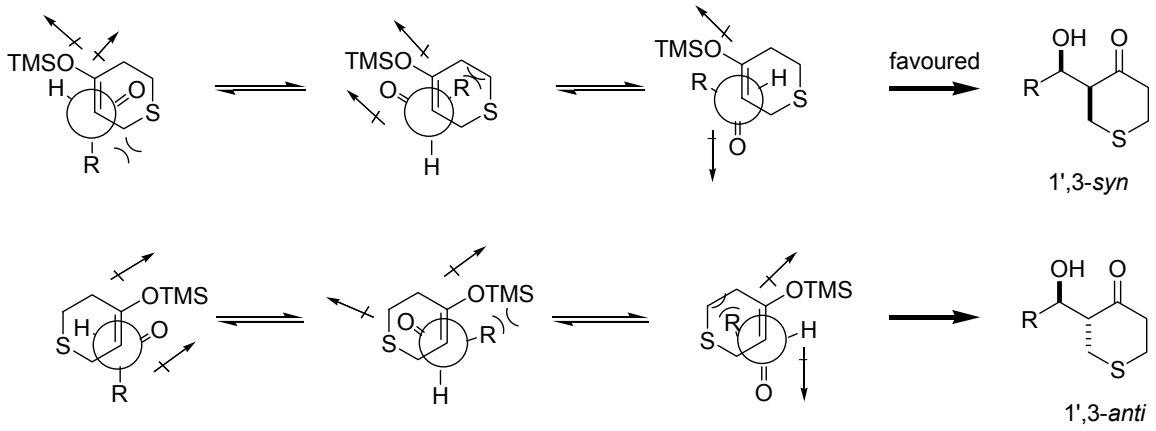


Figure 25: Sales' proposed 'open' transition state model for BF_3▪Et_2O and $TiCl_4$ promoted aldol reaction of **117** with **119.**[150]

In contrast, the reaction of **117** with **119** mediated by $SnCl_4$ gave the 1',3-*anti*-1',6''-*syn* product **120as** as the major adduct (Table 9 entry 2**)**. The *anti*-selective aldol topicity was accounted for by a proposed 'closed' transition state model (Figure 26) in which a chloride from the $SnCl_4$ removes the silyl group

[§] Determination of the relative configurations in the products is discussed in section 2.6

thereby facilitating the reaction.[151] The aldehyde face selectivity is accounted for using the Felkin model.

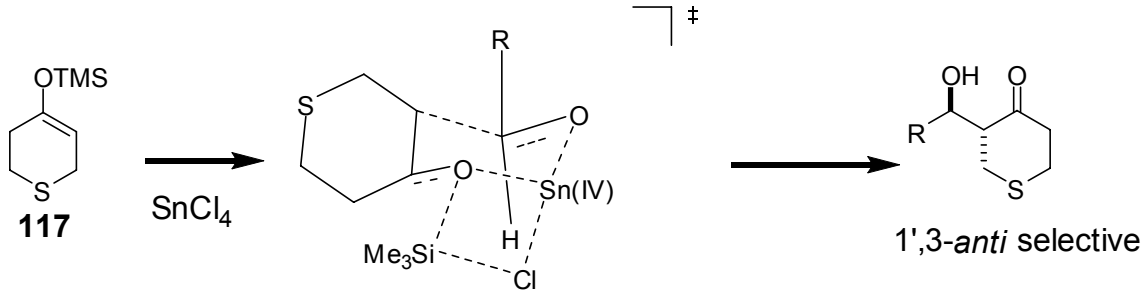
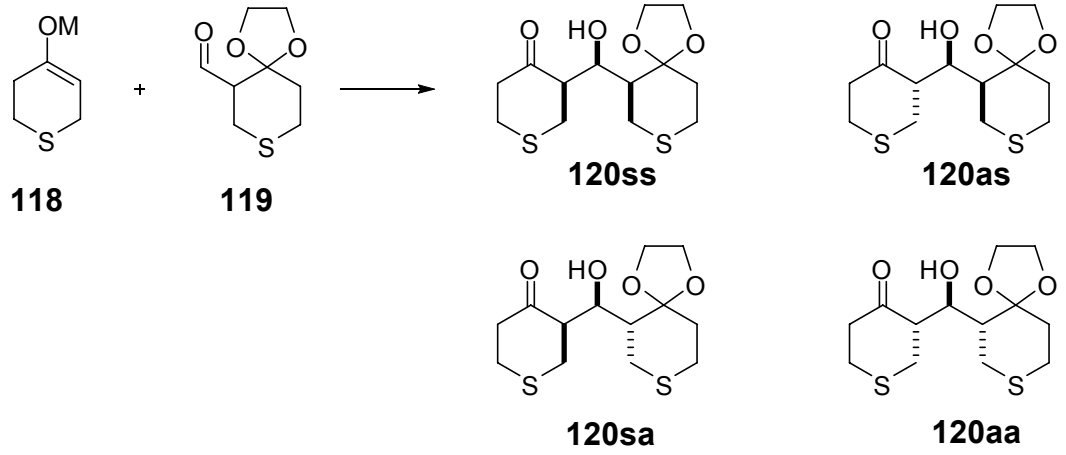


Figure 26: Proposed 'closed' transition state model for the $SnCl_4$ mediated reaction of **117** with an aldehyde.

Table 9: Summary of aldol coupling of **119** and **117** or **118**



			120	
Entry[a]	M	Lewis acid	**ss : as : aa : sa**	yield %
1	$SiMe_3$	$TiCl_4$	16 : 1 : - : -	87
2	$SiMe_3$	$SnCl_4$	1 : 3 : - : -	72
3	$SiMe_3$	BF_3▪OEt_2	2 : 1 : - : -	70
4	$SiMe_3$	$MgBr_2$ ▪OEt_2	- : - : 1 : 3.5	84
5	Li	-	1 : 9 : - : -	40
6	$TiCl_3$	-	3.6 : 1 : - : -	46
7	$B(Chx)_2$	-	1 :15 : - : -	84

Interestingly, the reaction of **169** (M =TMS) with **119** mediated with $SnCl_4$ (Table 8 entry 2) proceeds with high diastereoselectivity to afford the 1',3-*syn*-1',6''-*syn* product **170ss** suggesting that the reaction occurs via an 'open' transition state rather than a 'closed' transition state in contrast to the result obtained under similar conditions between **118** and **119**. The reaction of the Sn (II) enolate of **169** (M = SnOTf) with **119** gave the 1',3-*syn*-1',6''-*syn* product **170ss** selectively in 50% isolated yield[**] (Table 8, entry 7). The *syn*-selective aldol topicity of this reaction coupled with the result from the Mukaiyam aldol[114] of **169** (M = TMS) with **170** mediated with $SnCl_4$ is in sharp contrast to the trend observed by Denmark[151] and within the Ward group.[20-22] The reason why the relative aldol topicity is reversed in reactions of **119** with **117a** (M = TMS) and **169** (M = TMS) not fully understood at this time.

The $MgBr_2 \cdot Et_2O$ mediated reaction of **169** (M = TMS) with **119** (Table 8 entry 4) gave a moderate diastereoselectivity in that 2 of the 4 possible products were obtained. The 2 products 1',3-*anti*-1',6''-*anti* **170aa** and 1',3-*syn*-1',6''-*anti* **170sa** obtained from the reaction can be accounted for by the chelation control model proposed for the similar reaction between **118** (M = TMS) and **119** (Table 9 entry 4).[22] Attempts to improve the stereoselectivity between **170sa** and **170aa** by screening the effect of solvents[152] and the number of equivalents of the Lewis acid[150] did not meet with any success. The use of Me_2AlCl (Table 8, entry 5), as reported by Evans[153,154] for chelation controlled aldol reaction to mediate the reaction of **169** (M= TMS) with **119**, gave **170sa** and **170aa** in a similar ratio to that obtained with $MgBr_2 \cdot Et_2O$.

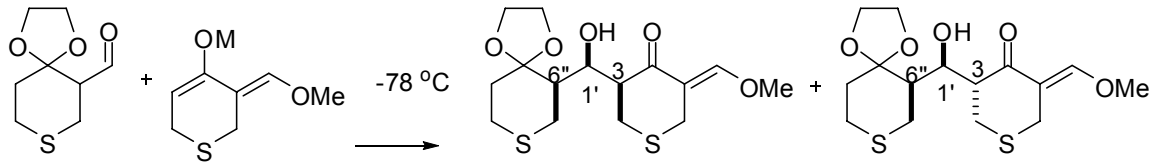
The reaction of the titanium enolate **169** (M = $TiCl_3$) generated from the reaction of **157** with $TiCl_4$ and (–)–sparteine[155] (Table 8, entry 6) gave the 1''3-syn-1',6''-syn aldol adduct **170ss**. The diastereoselectivity of this reaction is similar to what was observed for the analogous reaction of **118** (M = $TiCl_3$) with **119** (Table 9, entry 6).

The aldol reaction of **169** (M = Li) generated from the reaction of **157** with LDA with **119** gave poor diastereoselectivity and 3 out of the 4 possible products

[**] The yield reported is un-optimized.

were observed (Table 8, entry 14). Repeating the reaction using **169** (M = Li) generated under 'amine free' conditions did not improve the diastereoselectivity. This reaction is in contrast to the result obtained for a similar reaction between **118** (M = Li) and **119** (Table 9 entry 5) in which the 1',3-*anti*-1',6''-*syn* aldol adduct **120as** was formed with good diastereoselectivity. The aldol relative topicity of this reaction (Table 9, entry 5) was rationalized using the Zimmerman-Traxler 'closed' transition state model[22,122]. The reaction of the boron enolate of **169** (M = Chx_2B, generated from the reaction of **157** with Chx_2BCl using Et_3N) with **119** gave **170as** with good selectivity (Table 8 entry 8) consistent with the result obtained under similar conditions when **118** (M = Chx_2B) and **119** (Table 9, entry 7). The shorter B-O bond[156,157] has been invoked to account for why boron enolates gives higher stereoselectivity in aldol reactions when compared to lithium enolates. Optimization (Table 10) of the reaction of the boron enolate **169a** with **119** revealed that the reaction was sensitive to the condition for the generation of the enolate. The choice of base, enolate generation time, and reaction temperature greatly affected the yield and stereoselectivity of the reaction. The wide variation in the yield of the aldol adduct **170as** obtained from these reactions can be rationalized to be the result of enolate decomposition at 0 ^{o}C and incomplete enolate formation at -78 ^{o}C. At -40 ^{o}C, complete formation of the enolate occurs within 1 h with little or no decomposition leading to the observed improvement.

Table 10: Summary of optimization study on the aldol coupling of **119** and **169a**



119 **169** M = $B(Chx)_2$ **170ss** **170as**

Entry	Base	Temp* (°C)	**170ss : 170as**	yield %
1	DIEA	-78	1 : 9	40
2	Et_3N	-78	1 : 9	50
3	Et_3N	0	1 : 9	63
4	Et_3N	-40	1 : 12	78

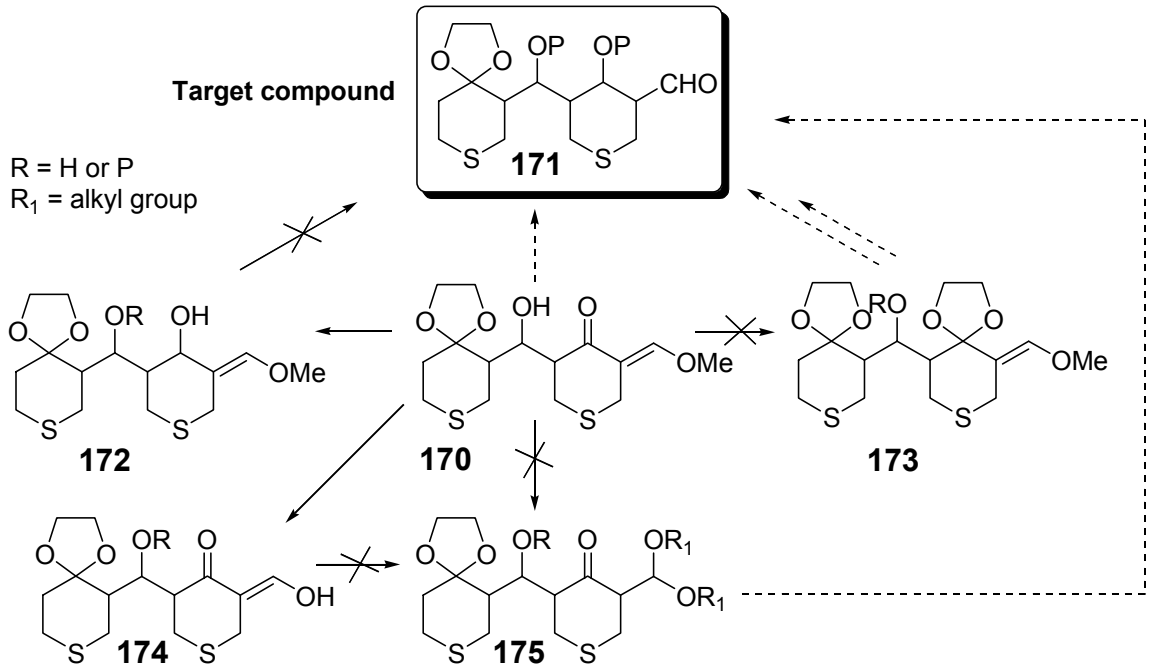
* Temperature at which enolate was generated

The diastereoselectivity of the reaction of **169** (M = Chx_2B) with **119** is comparable with the observed stereoselectivity from the reaction of **118** (M = Chx_2B) with **119** (Table 9, entry 7). The anti-selective aldol relative topicity was rationalized using the Zimmerman-Traxler[122] 'closed' transition state model.

In conclusion, the aldol reactions of different enolates of **157** with **119** generally proceeded with lower diastereoselectivity when compared to the reactions of **112** with **119** under the same reaction conditions. This modulating effect of the methoxymethylediene group in **157** on the aldol reactions of the corresponding enolates might be due to the increased reactivity (vinylogous ester) and/or conformational effects. Also all the four possible diastereoisomers were synthesized selectively if the geometry of the exocyclic the enol group is disregarded.

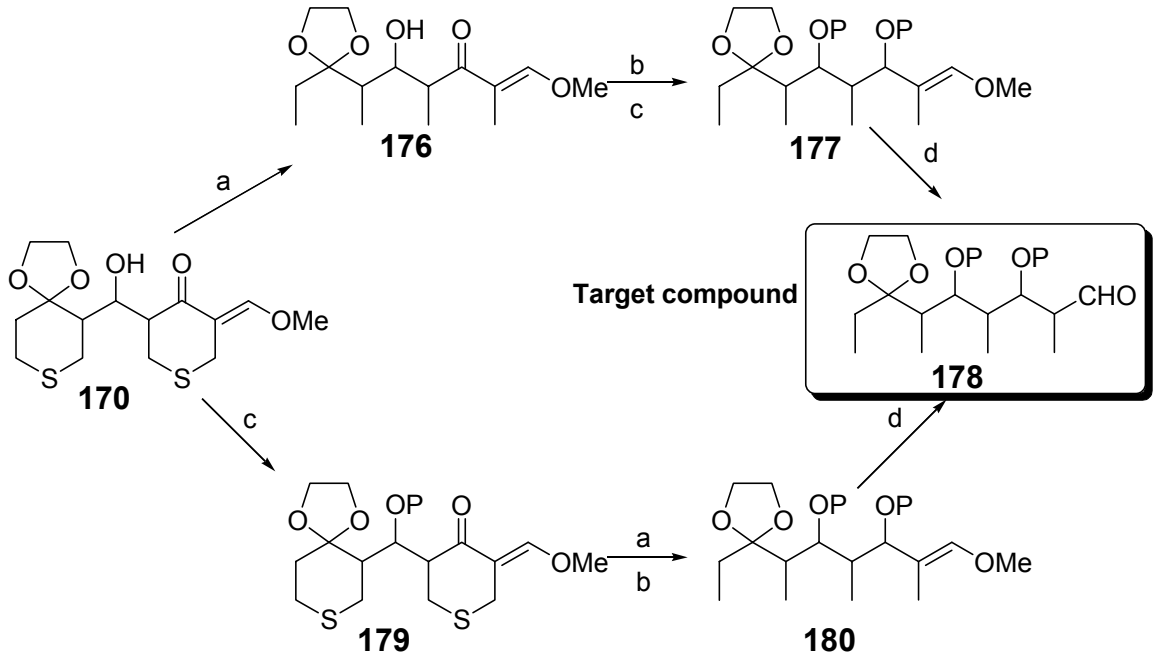
2.3.5 Attempted functional group transformation of the aldol adducts 170.

With the conditions to access all the four possible diastereoisomers of **170** established, the next objective was to find ways to transform these adducts into an aldehyde suitable for a second aldol coupling (Scheme 25).



Scheme 25: Approaches to derivatizing aldol adducts **170** for further aldol couplings

A second objective was to transform the diastereoisomers of **170** into tetrapropionate fragments by desulfurization of a suitable derivative and appropriate functional group transformations (Scheme 26). Several approaches to achieve these objectives are discussed in the following sections.



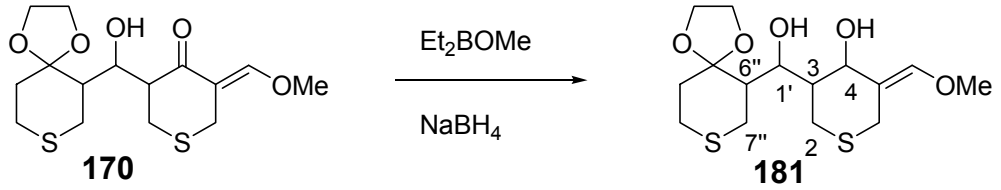
a) desulfurization; b) reduction; c) protection; d) hydrolysis**.**

Scheme 26: Approaches to transform the aldol adducts **170** to tetrapropionate fragments.

2.3.5.1 Attempted transformation of aldol adducts 149 into an aldehyde suitable for second iteration.

The first route to **171** that was investigated involved the hydroxyl group directed stereoselective reduction of the ketone in **170** using Et_2BOMe and $NaBH_4$[148,149] (Table 11). The yields and selectivities for the 1,3-*syn* diol adducts varies among the **170** diastereoisomers.

Table 11: stereoselective reduction of **170**



170 **181**

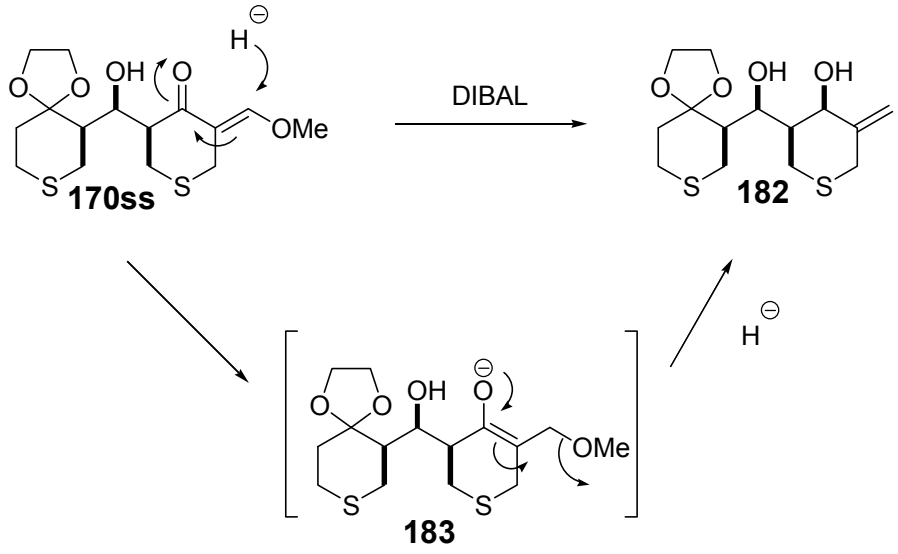
entry	substrate	product	1,3-syn:1,3-trans	% yield
1	**170as**	**181aas**	>20 : 1	88
2	**170aa**	**181aaa**	>10 : 1	46[a]
3	**170sa**	**181ssa**	15 : 1[b]	ND

a) un-optimized and isolated by PTLC.

b) ratio determined from ^{1}H NMR of crude.

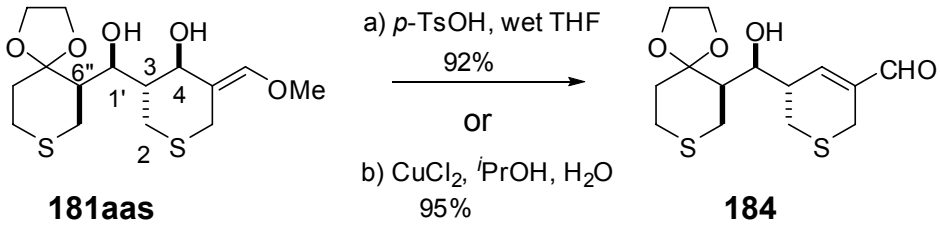
Similar reductions of adducts **170** with DIBAL in THF at -78^{o}C gave mixtures of products. In the case of the 1',3-syn-1',6''-*syn* aldol adduct **170ss**, the major product (52%) from the DIBAL reduction was the 1,3-*syn* diol **182**. This product presumably was the result of an initial 1,4-addition of the hydride followed by a second 1,2-addition (Scheme 27).

Attempts to form the 1,3-*anti* diosl by reduction of **170** using Evans[145] hydroxyl directed protocol proved unsuccessful as the aldol adducts **170** are not stable to acidic conditions and considerable hydrolysis of the methoxy protecting group occurred.



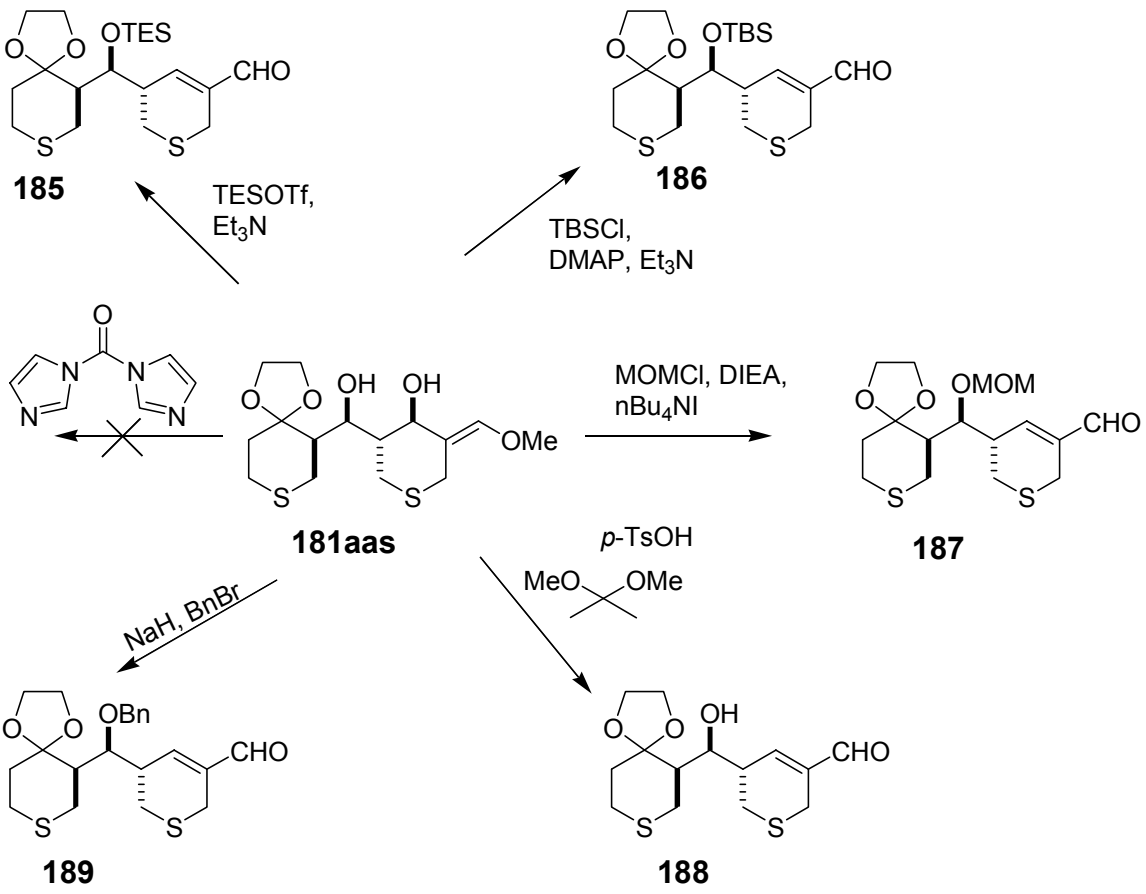
Scheme 27: Reduction of **170ss** with DIBAL

Attempts at hydrolysis of the methyl enol ether in the diols **181** to reveal an aldehyde group were unsuccessful despite considerable effort. In all cases, facile elimination was observed as illustrated for **181aas** (Scheme 28).



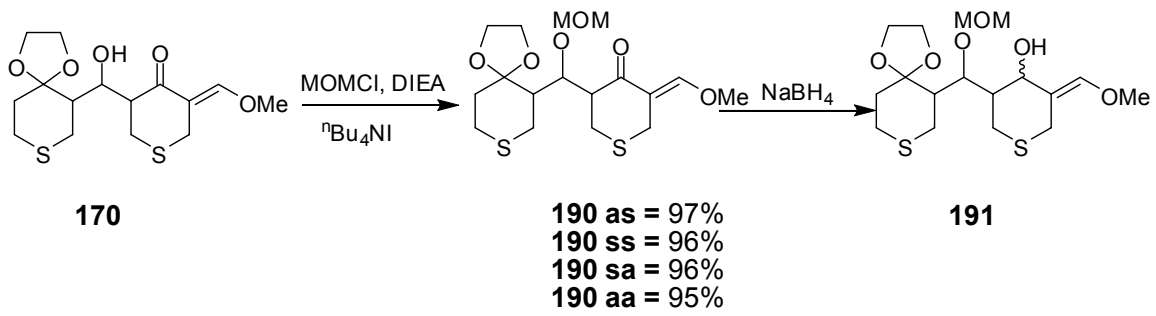
Scheme 28: Attempted hydrolysis of the methyl enol ether in **181aas**.

The inability to effect hydrolysis of the enol ethers in **181** prompted a series of attempts to obtain protected derivatives that might be better substrates for the hydrolysis. Unfortunately, in all cases, under a wide range of conditions and protecting groups, only the mono protected elimination products were detected as illustrated for **181aas** (Scheme 29). This suggests that the diol adducts have a high propensity for elimination of the C-4 hydroxyl group and as such this route to obtain **171** was abandoned.



Scheme 29: Attempted bis protection of **181aas**

An alternative route to **171** involving initial protection of the hydroxyl group in the aldol adducts **170** prior to reduction was next explored. The MOM protected derivatives **190** were prepared in good yields (95-97%) for the four adducts (Scheme 30).



Scheme 30: MOM protection of aldol adducts **170**.

Reduction of the MOM derivatives with $NaBH_4$ gave 1:1 mixtures of adducts **191** that could neither be protected nor hydrolyzed. Thus this route to **171** was also abandoned.

The next approach to **171** that was explored involved manipulations of the methyl enol ether group in an attempt to obtain a more suitable analogue. Attempts at forming acetal derivatives of **170** as illustrated with **170as** gave only retro-aldol products in all the cases investigated (Figure 27).

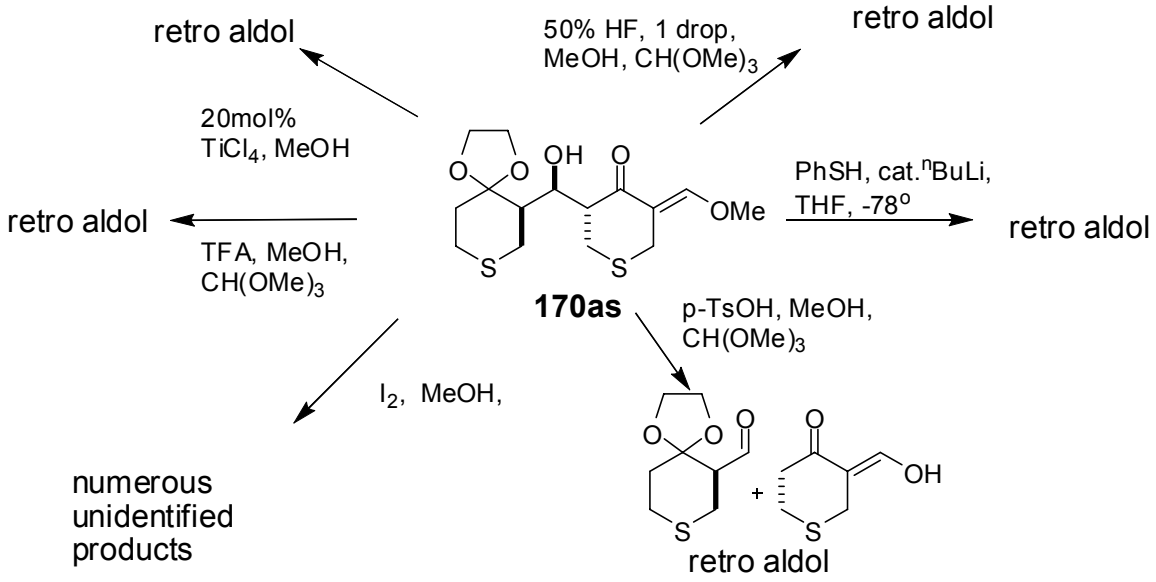


Figure 27: Attempts at preparing acetal derivatives of **170as.**

As a means of preventing the retro-aldol process in the reactions illustrated in Figure 27, the MOM protected derivatives **190** were next explored. Attempts to hydrolyze directly the methyl enol ether in **170** under acidic conditions gave only retro-aldol products. The use of the MOM protected derivative **190** under the same acidic condition furnished the hydrolyzed product **191as** in excellent yield (95% for **190as,** Figure 28).

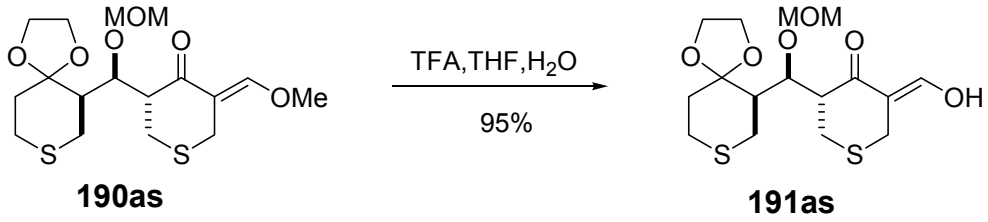
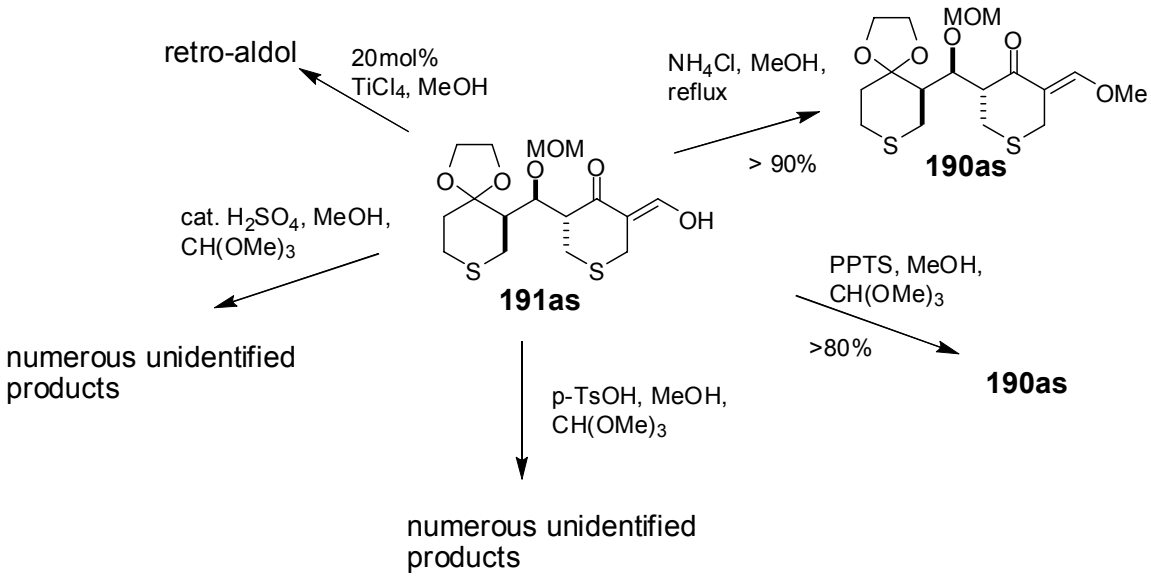


Figure 28: Hydrolysis of MOM protected **190as**

Attempts at protecting the aldehyde group in **191** (illustrated with **191as**) as the acetal gave retro-aldol products under strong acidic conditions in the presence of methanol and returned the methyl enol ether **190** under weak acidic conditions (Scheme 31).



Scheme 31: Attempts at preparing acetal derivatives of **170** from **191as**.

The use of alcohols other than methanol (e.g. ethanol and isopropanol) in the reactions illustrated in Scheme 31 only gave retro-aldol products. The use of diols (e.g. ethylene glycol), in an effort to form a cyclic acetal, under standard acid conditions or Noyori's condition[104] did not give products that could be characterized and both reactions were very messy. Attempts to carry out a chemoselective reduction of the keto-enol **191as** also were not successful as both groups were reduced in a non-stereoselective manner.

2.3.5.2 Attempted transformation of aldol adducts 170 into tetrapropionate units.

The second objective for the use of the aldol adducts **170** involves their transformation into tetrapropionate units that could be applied in total synthesis of natural products. Stereoselective reduction of the ketone group in **170,** hydrolysis of the methyl enol ether followed by desulfurization will afford the desired derivative **178** (see Scheme 26). The stereoselective reduction of **170** was achieved but attempts to hydrolyze the methyl enol ether in both **170** and its derivatives did not meet with any success (see discussion in the preceding section).

Attempts at desulfurization of the aldol adduct **170** (**170as** and **170ss**) and the derivatives **181**aas, **190as**, **190sa** and **191as** were not successful. Analysis of the ^{1}H NMR spectrum of the crude reaction mixtures in all cases revealed mixtures of several compounds. Despite considerable experimentation involving various modifications to the reaction conditions, including the use of additives[158] the desired desulfurized adducts were not obtained in any appreciable yield.

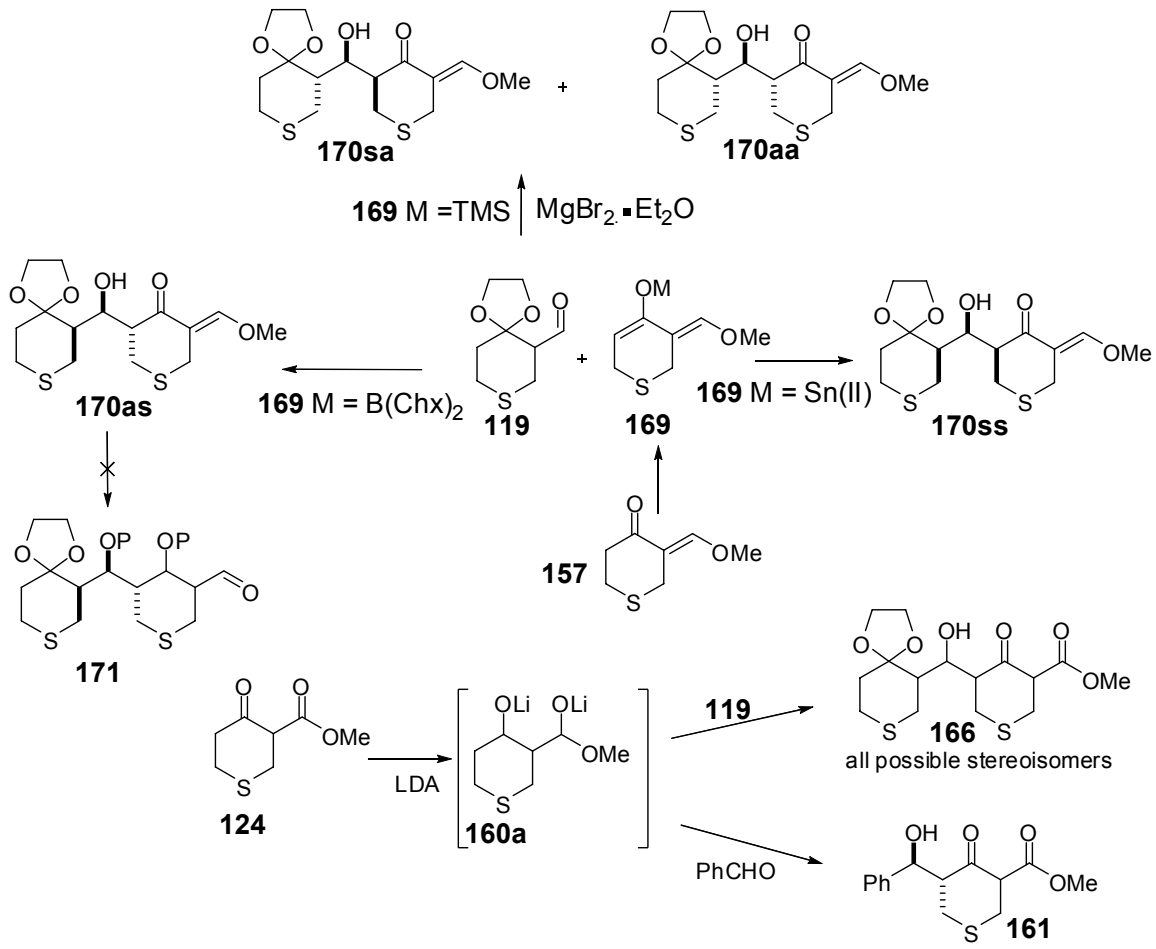
2.3.6 Summary and conclusions

Two β-ketocarbonyl derivatives of thiopyranone (**124** and **157**) were successfully synthesized and their aldol reactions with the thiopyran aldehyde **119** were shown to occur at the γ-position.

The dienolates generated from **124** gave aldol adducts with *anti* diastereoselectivity which is consistent with an *E* enolate in a Zimmerman-Traxler[122] type 'closed transition state'. Reaction of **119** with the dilithium dienolate generated from the reaction **124** with LDA gave a good overall yield of aldol adducts but with poor diastereoselectivity as all four possible diastereoisomers were detected.

All four possible aldol adducts **170** from the reaction of the **157** with **119** were successfully prepared. The aldol adduct **170as** was obtained selectively from the reaction of the boron enolate **121** with **119** and **170ss** was obtained selectively from the reaction of **119** with the Ti(IV) or Sn(II) enolate of **157** or from the $SnCl_4$ promoted reaction of **158** with **119**. These two adducts (**170**as and **170**ss) results from a 'Felkin' addition to the aldehyde **119.** The diastereoisomers **170sa** and **170aa** results from an 'anti Felkin' addition to the aldehyde **119** and were obtained from the $MgBr_2 \cdot Et_2O$ mediated reaction of **158** with **119**. Although the stereoselectivityof this reaction was low (1.5:1, in favor of **170sa**), a combination of isomerization (see section 2.6) and fractionation could give either adduct in good overall yield.

Attempts to transform aldol adducts **170** (or derivatives) into aldehydes (e.g. **171**) suitable for a second aldol coupling did not meet with any success. Likewise, despite considerable experimentations, the aldol adducts **170** (or derivatives) could not be transformed into tetrapropionate units suitable for natural product synthesis (Scheme 32).



Scheme 32: Summary of the second approach in the thiopyran route to polypropionates

2.4 Simultaneous two directional aldol additions and desymmetrization by enolization.

2.4.1 Introduction

One of the proposed routes to a hexapropionate fragment via the thiopyran-based methodology involves a two-directional aldol reaction of the *meso* dialdehyde **115** (Figure 11, route 2). If both additions could be achieved in a sequence not involving separation of the mono adduct prior to the addition of the second unit, this would be a very efficient process (Figure 29).

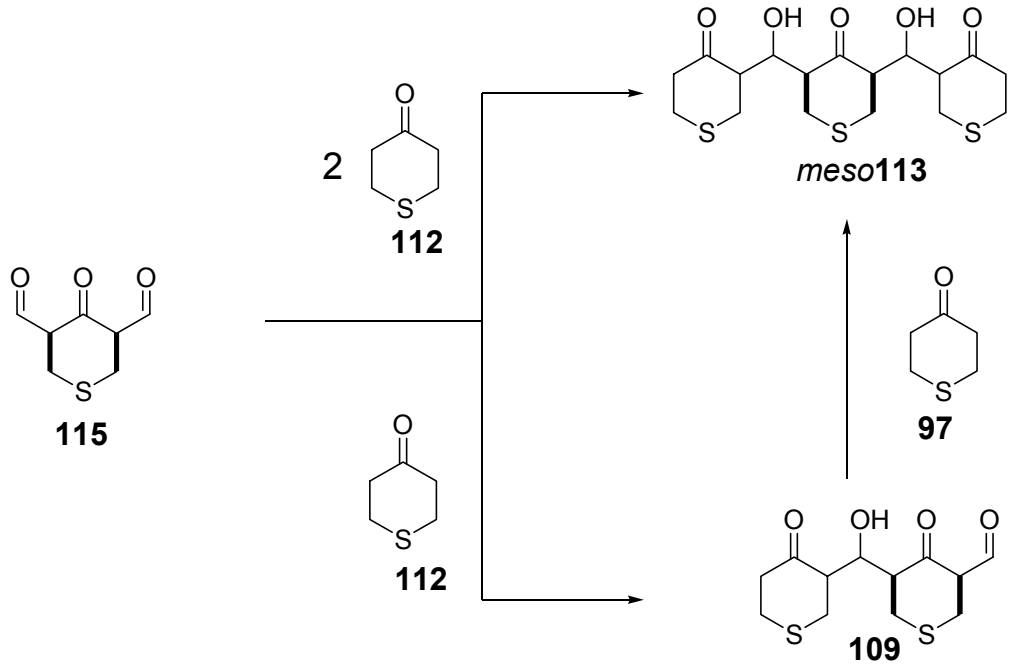


Figure 29: Proposed sequential and/or simulatneoues double addition to a *meso* dialdehyde

This double addition in a single pot is referred to as simultaneous two-directional aldol additions.[63,66,103] The *meso* diketone **113** thus obtained would need to be differentiated and functionalized (one carbon must be added) to

afford a chiral nonracemic hexapropionate fragment. The choice of reaction to employ for desymmetrization of **113** diketone is dependent on a number of factors:

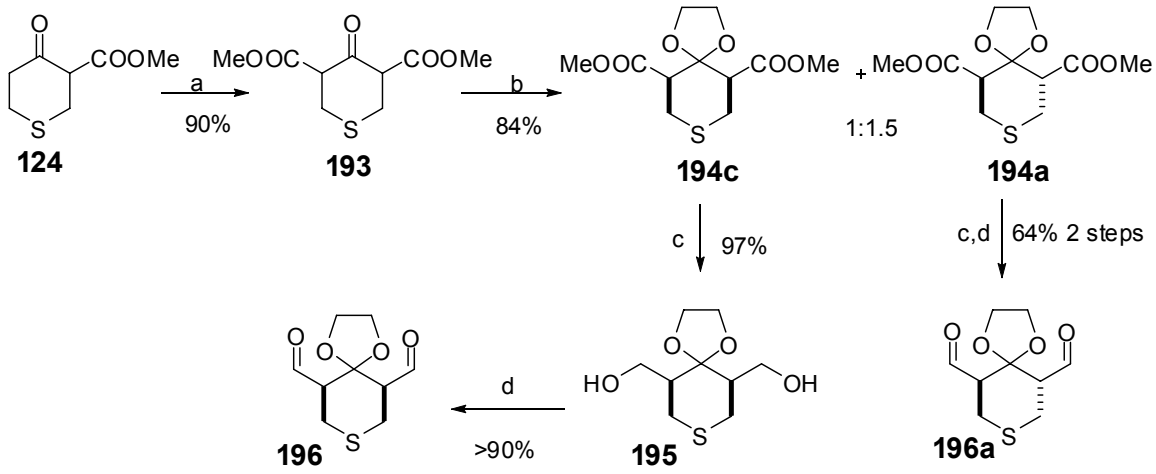
i) The process should allow for the product obtained to be usable in more than one reaction type, ii) the products generated from the reaction should be easily transformed back to the starting material. Selective enolization of the ketone groups followed by trapping the enolate as the silyl enol ether would fulfill the above conditions. Desymmetrization of achiral or *meso* cyclic ketones using chiral lithium amides is a well established process.[159-162] Adapting this process to a *meso* diketone has been an ongoing objective within the Ward group.[163] One advantage of this approach is that enhanced levels of enantiomeric purity can be achieved even from reactions with modest selectivity. This enhancement occurs because of the coupling of initial asymmetric synthesis with a subsequent kinetic resolution when the enantiotopic group can react sequentially.

The first focus of this study is the synthesis of a practical analogue of *meso* **114**. The high diastereoface selectivity associated with addition to the ketal protected aldehyde **119** makes the ketal protected *meso* dialdehyde **196** a possible candidate (Scheme 32).

2.4.2 Synthesis of (6*R*,10*S*)-1,4-Dioxa-8-thiaspiro[4.5]decane-6,10-dicarboxaldehyde (196) and (3*R*,4*s*,5*S*)-tetrahydro-4(methoxy methoxy)-2*H*-thiopyran-3,5-dicarboxaldehyde (200).

Carboxylation of the β-ketoester **124** afforded the β-ketodiester **193** in good yield (Scheme 33). A careful addition of the chloroformate to the lithium dienolate of **124** generated with LDA while maintaining the reaction temperature below -70 ^{o}C minimizes formation of the O-acylation product. Attempts to protect the ketone group in **193** under standard acid catalyzed conditions were not successful. Ultimately, the ketal protection under Noyori's condition[104] gave **194**

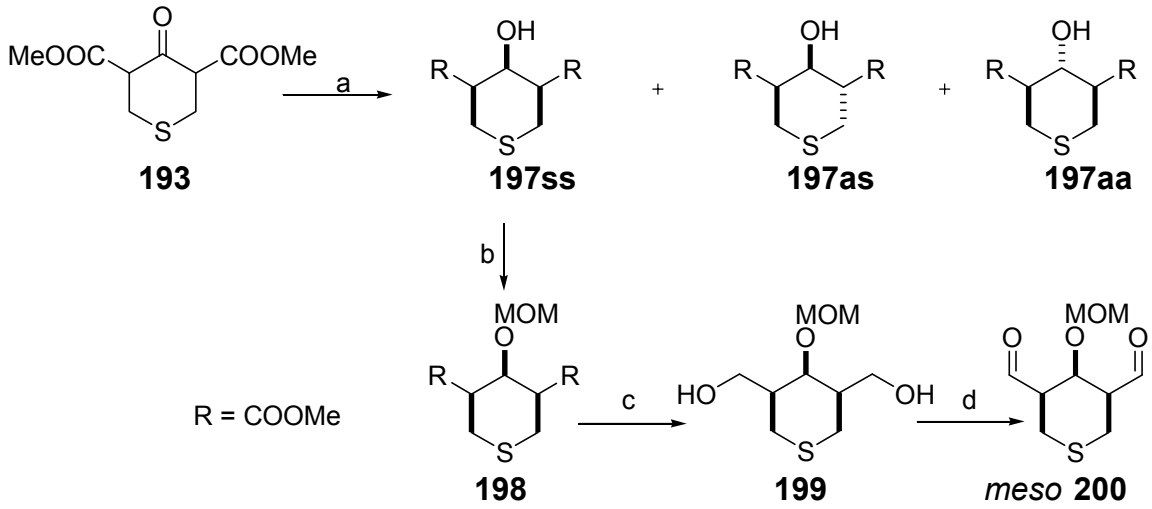
as a separable 1:1.5 mixture of **194c** and **194a**, respectively. Reduction of **194c** with $LiAlH_4$ followed by a modified Swern oxidation[106] with a non-aqueous work up[77] furnished the desired *meso* dialdehyde **196** in good yield. Attempts to fractionate the product by SiO_2 chromatography always led to an inseparable mixture of the C_s and C_2 symmetric stereoisomers of the dialdehyde. Thus, the crude product was used directly.



Scheme 33: Preparation of the ketal meso dialdehyde **196**.

a) 3 equiv. LDA, THF, -78 °C, 1 h/ 1 equiv. ClCOOMe, -78 °C, 1 h; b) 0.5 equiv. TMSOTf, 1.5 equiv. $TMSOCH_2CH_2OTMS$, $CHCl_3$, reflux, 24-48 h; c) 2 equiv. LAH, THF, RT, 40 min; d) 2.1 equiv. $(COCl)_2$, 4.2 equiv. DMSO, 4 equiv. DMS, 6 equiv. DIEA, DCM, -78 °C, non-aqueous workup.

Preparation of the *meso* dialdehyde **200** from **193** was uneventful (Scheme 34). A non-selective reduction of the ketone group in **193** using $NaBH_3CN$ gave **197** as a 6:4:1 mixture of the three possible stereoisomers with the all *cis meso* isomer **197ss** being favored.



a) 1.5 equiv. $NaBH_3CN$, 1 equiv. citric acid, EtOH: DCM (1:1), -10→ 9 ^oC over 5h (80% combined); b) 5 equiv. MOMCl, 7.5 equiv. DIEA, 1 equiv. $^nBu_4NI$, DCM, 24h rt (97%); c) 3 equiv. $LiAlH_4$, THF, rt, 1h, (95%); d) 2.1 equiv. $(COCl)_2$, 4.2 equiv. DMSO, 4.2 equiv. DMS, 6 equiv. DIEA, -78 ^oC, non-aqueous-work up (93%).

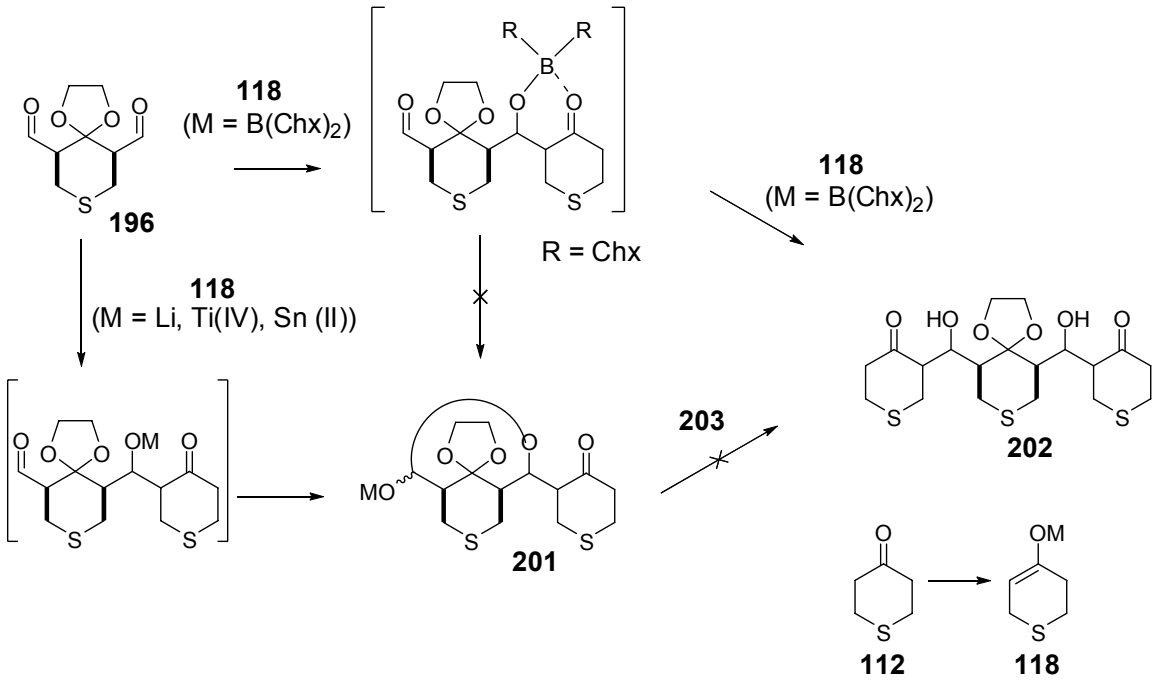
Scheme 34: Synthesis of meso dialdehyde **200**

Conversion of **197ss** to the corresponding MOM derivative **198** followed by reduction of the ester groups with $LiAlH_4$ furnished the *meso* diol **199** in excellent yield. Subjecting the diol **199** to a modified Swern oxidation protocol[77] with a non-aqueous workup provided the desired *meso* dialdehyde **200**. Attempts to separate the other *meso* diester **197aa** from the C_2 symmetric **197as** were not successful.

2.4.3 Simultaneous two directional aldol additions to *meso* dialdehydes 196 and 200.

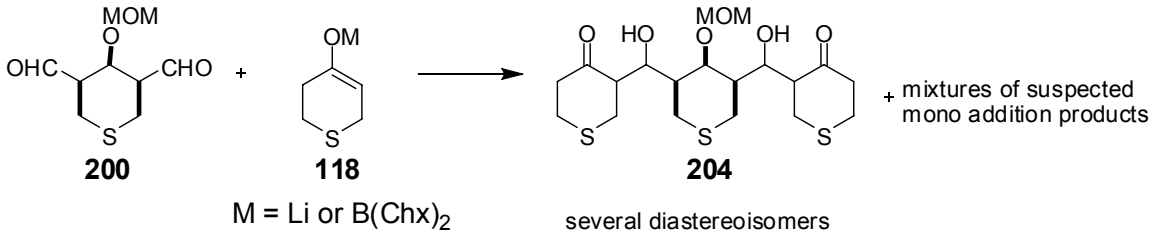
With the two *meso* dialdehydes **196** and **200** in hand, their reactions with various enolates of **112** were investigated to assess the possibility of a simultaneous double aldol addition. The goal was to find conditions that would favor the formation of a *meso* hexapropionate bisaldol adduct that ultimately would be desymmetrized via enantioselective enolization.

The choice of a boron enolate of thiopyranone (**112**) to investigate the possibility of a double addition to the dialdehydes **196** and **200**, despite the reports of Oppolzer *et al.*[68,75,77], was easily reached. The formation of a stable hemiacetal intermediate from the first addition would prevent the second aldol (*c.f.* **201**→ **202**)**.** Thus the use of an enolate that would produce an aldol adduct less likely to form the hemiacetal is required. Aldol reactions of enol borinates are known to give aldol borinates that must be hydrolyzed during the workup (often requiring oxidation) (Scheme 35).



Scheme 35: Single and double addition of thiopyran enolates to *meso* dialdehyde **196**.

Addition of 3 equiv. of the boron enolate **118** (M = $B(Chx)_2$) to the *meso* dialdehyde **200** afforded a complex mixture of products (Figure 30). Analysis of the ^{13}C NMR spectrum of the crude reaction mixture indicated the presence of a minimum of 11 different carbonyl groups, indicating that the aldol addition was not diastereoselective. HPLC analysis of a homogenous sample (by TLC) of the reaction product revealed a minimum of 12 distinct compounds. Similarly, the addition of the lithium enolate **118** (M = Li) to the *meso* dialdehyde **200** gave identical results. The high number of products obtained from these two reactions and the fact that the products cannot be separated by FCC makes the *meso* dialdehyde **200** not suitable for the study of the proposed route 3 in Figure 11.



Scheme 36: Aldol addition **118** to **200.**

Reaction of the *meso* dialdehyde **196** with a slight excess of the lithium enolate **118** (M = Li) afforded the expected mono addition product **201ass** as a mixture of hemiacetals with the 1',3-anti-1',6''-syn relative configuration (see section 2.6). Addition of 3 equiv. of the enolate improved the yield of **201ass** to 40% but without any trace of bis addition product (Figure 30).

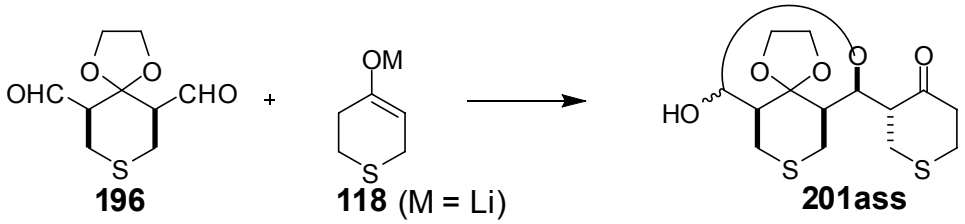
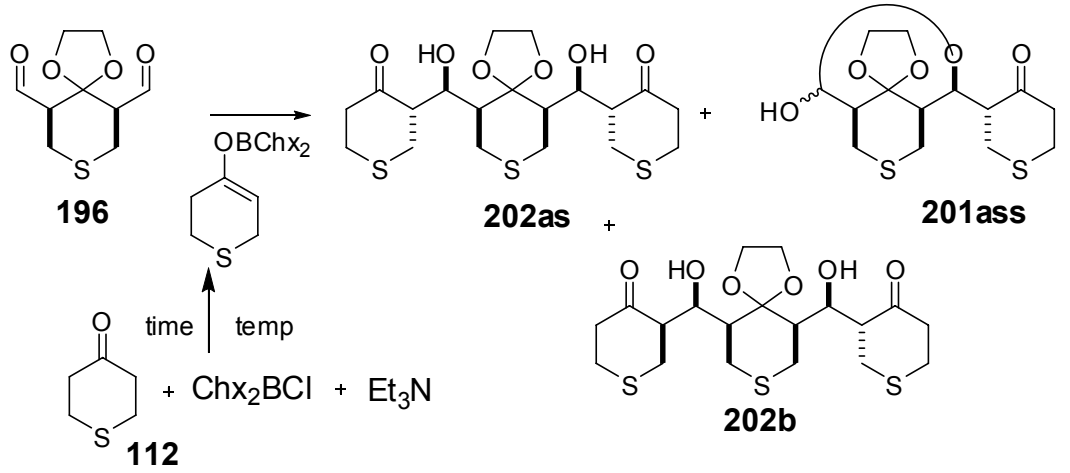


Figure 30: Addition of lithium enolate to *meso* dialdehyde **196**

Reaction of **196** with 1.2 equiv. of the boron enolate **118** (M = $B(Chx)_2$) gave mainly the mono addition product **201ass** but, in contrast to the reaction with the lithium enolate **118**, a small amount of the bis addition product **202** was detected. The use of more that 2 equiv. of the enolate led to the formation of two bis aldol products in a 6-7:1 ratio along *ca* 10% of the mono addition product **201ass**. The results of optimization studies on the reaction are summarized in Table 12.

The reactions were carried out on 0.23 mmol scale with respect to the *meso* dialdehyde **196**. It is interesting to note that Et_3N is a more effective base for the generation of the enolate compared to DIEA or (-)-sparteine [This observation is similar to what was observed for the generation of boron enolates of the thiopyranone analogue **157** (see section 2.3.4)]. A short reaction time gave only the mono addition product (Table 12, entry 9), suggesting that the rate of the addition of the second enolate is slow compared to the first and this would account for why enolates that produce lactol forming aldolates would furnish only the mono aldol product. The reaction is sensitive to the conditions for the enolate generation. The optimum condition that was amiable to scale up (*ca.* 2 mmol of *meso* dialdehyde **196**) involved generating the enolate at 0 ^{o}C for 30 min and then cooling to -78 ^{o}C for another 30 min prior to the addition of the dialdehyde. The relative configuration in the major product **202as** obtained is as expected from the addition of an *E*-enolate via a 'closed' transition state to the ketal protected aldehyde **119** (see section 2.3.4). The determination of the relative configurations in the all the aldol adducts obtained from the reaction above is discussed in section 2.6.

Table 12: Summary of optimization study on the double addition.



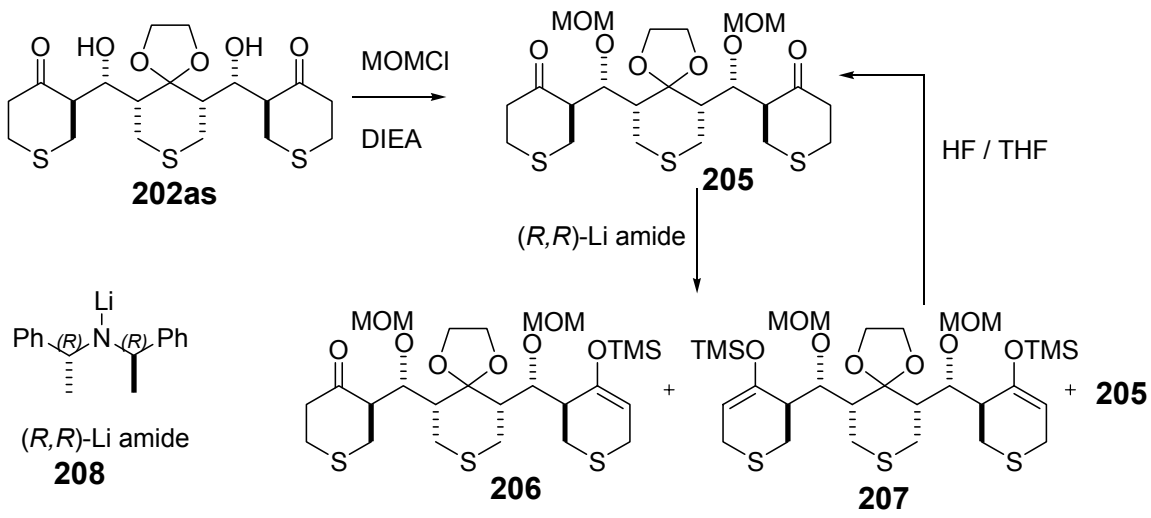
entry	enolate equiv	enolate generation time/h	reaction time/h	% yield 202as	202b	201ass
1	1.2 [a]	0.5	2	trace	-	40
2	3 [a,b,c]	2	3	38	9	10
3	4.8 [a]	0.5	3	35	7	8
4	3 [d]	0.5	5	21	-	7
5	3 [d]	1	3	30	2	12
6	3 [d,e]	1	3	3	4	11
7	3 [d,f]	1	3	9	trace	10
8	4 [b,d,g,h]	0.5	3	44	6	11
9	4 [d,g,h]	0.5	1	-	-	70
10	4 [d,g,h]	0.5	3	56	8	8
11	4 [d,g,h,i]	0.5	3.5	50	8	10

a) Enolate generated as stock solution in hexanes + DCM; b) enolate generated at -78 ^{o}C; c) the enolate was transferred by cannula at -78 ^{o}C; d) Freshly prepared Chx_2BCl used neat; e) DIEA used as base for enolate generation; f) (-)-sparteine used as base for enolate generation; g) after the enolate was generated at 0 ^{o}C, it was cooled to -78 for 30min; h) the enolate was generated by adding Chx_2BCl to the ketone in solution and then adding the base; i) reaction on 2 mmol scale.

2.4.4 Desymmetrization of *meso* diketone 202as by enantioselective enolization.

Differentiation of the enantiotopic ketone groups in the *meso* bis aldol **202as** obtained from the simultaneous double aldol addition reaction was achieved via enantioselective enolization followed by trapping the enolate as the silyl enol ether. This approach was developed[163] within the group and its successful application to this substrate contributes to the generality of the approach. The protection of the meso bis aldol **202as** as its bis MOM ether analogue **205** was not very smooth as the reaction stops at low conversion(<35% bis protected product) despite long reaction time (3 days) and high concentration. The recovered mono protected product was re-subjected to the protection reaction to ultimately afford the bis MOM analogue **205** in 59% isolated yield. This process can be repeated a few times to improve the overall conversion. The reason why the reaction tends to stop at low conversion even with prolonged reaction time (>10 days) is not understood at the present time.

Addition of 1.4 equivalent of chiral lithium amide **208** to a solution of **205** containing TMSCl at -100 ^{o}C afforded the desymmetrized product **206** in 71% yield with a 95% ee. The bis enol silyl ether **207** was also isolated in 17% (Scheme 37).



Scheme 37: Desymmetrization of MOM protected *meso* bis aldol **205**

The mono silylated product **206** was not stable to storage due to the easily hydrolyzable TMS group and was subjected to a stereoselective reduction with L-selectride and, hydrolysis of the silyl enol ether on work up furnished the stable hydroxyl ketone **209** in 88% yield (Figure 31).

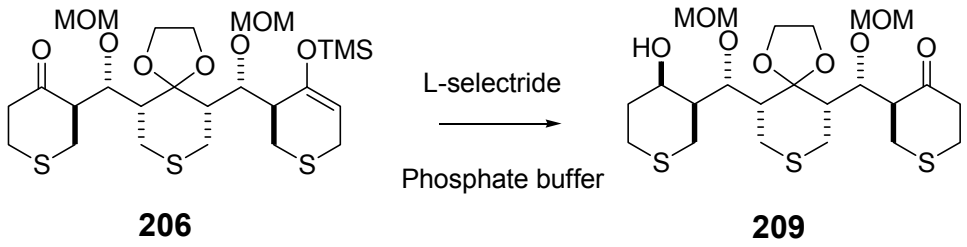


Figure 31: Stereoselective reduction of **206**

The desymmetrization process is very efficient in that the bis enol ether **207** can be easily recycled by HF promoted hydrolysis to give the bis MOM diketone **205** in >95% yield.

2.4.5 Summary and conclusions.

Two stable *meso* dialdehydes **196** and **200** were synthesized and their use in simultaneous two-directional aldol additions were investigated. The *meso* dialdehyde **196** was successfully converted to a *meso* bis aldol adduct **202as** with six stereogenic centers in a one pot reaction in 50% isolated yield. Employing the methodology developed in the group,[163] the *meso* diketone **205** was successfully desymmetrized via an enantioselective enolization reaction to afford the chiral mono enol ether **206** in 71% isolated yield (>95% based on recovered **205**) with 95% ee.

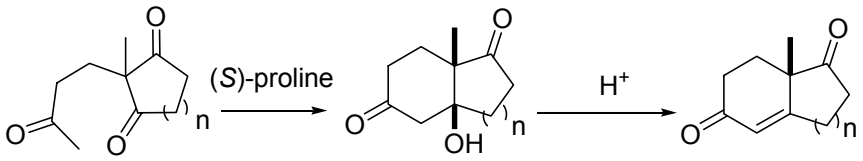
2.5 Enantiotopic group selective aldol reaction using proline as catalyst.

The concept of desymmetrization of *meso* compounds is a well researched one.[63,164] In keeping with the theme of this research, desymmetrization of *meso* dialdehydes using various reaction types was discussed in section 1.2. Of particular interest, is the use of an enantiotopic group selective aldol reaction by Oppolzer and co-workers[68,75,77] in their synthesis of polypropionate containing natural products (see Scheme 7, Section 1.2.2.5). Their process involved the use of a chiral auxiliary attached to the enolate to achieve enantioselectivity. The development of a direct intermolecular enantiotopic group selective aldol reaction is described below.

2.5.1 Proline-catalyzed direct aldol reactions.

Stereoselective 'direct' aldol reaction of unmodified ketones and/or aldehydes have emerged as a powerful method in recent years.[165] Methods based on enzymes, antibodies, organometallics and organocatalysis have been applied to good success. Organocatalysis of the 'direct' aldol reaction of unmodified ketones and/or aldehydes has been extensively researched over the past five years. Since the landmark paper published by List, Lerner and Barbas in 2000,[60] proline and its derivatives have been used to catalyze direct aldol and many other reactions to afford adducts with high diastereo and enantioselectivity.[61,165]

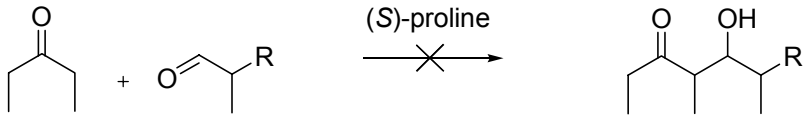
The use of proline as a catalyst for the aldol reaction was first reported in the context of an intramolecular reaction (Scheme 38).[166,167] Triketones **210** were subjected to (*S*)-proline under various reaction conditions to afford **211** and/or **212** with ee's ranging from 71-93%. The aldol products **211** and **212** are precursors for the synthesis of various natural products including steroids.[167]



210 **211** **212**

Scheme 38: First example of proline catalyzed direct aldol reaction.

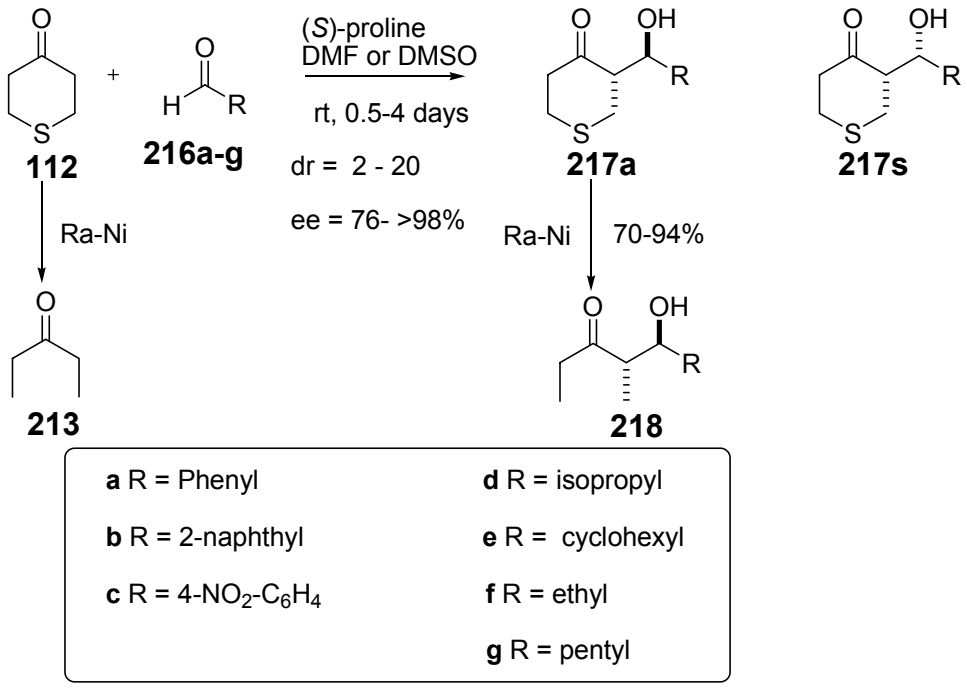
Although the proline catalyzed direct intermolecular aldol reaction has been well studied[61,165] within the last 5 years, the substrate scope has been very limited in terms of the ketones used and the synthetic utility of the adducts obtained. A limitation to the application of this process to the preparation of enantioenriched fragments for the synthesis of polypropionates is the lack of reactivity of 3-pentanone and other ethyl ketones (Figure 32).[61,165]



213 **214** **215**

Figure 32: 3-Pentanone unreactive in the presence of (*S*)-proline.

As a way to solve the reactivity problem of 3-pentanone and in keeping with the Ward group's research theme of thiopyran-based route to polypropionates, the proline catalyzed direct aldol reactions of tetrahydro thiopyran-4-one **112** with simple aldehydes was investigated (Scheme 39).[168]

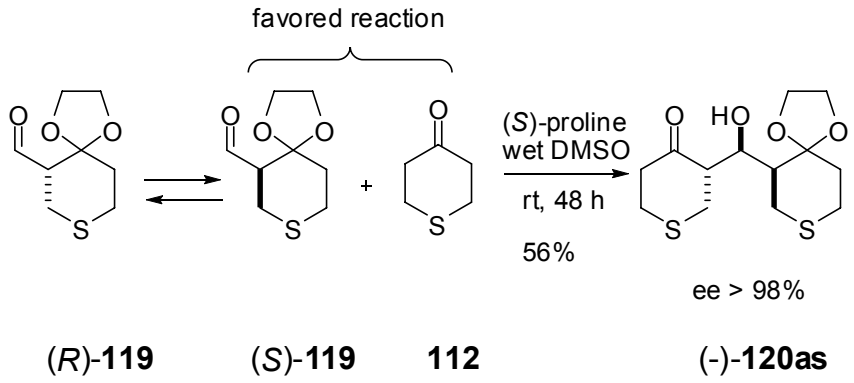


Scheme 39: Proline catalyzed direct aldol reaction of thiopyran-4-one with various aldehydes

The results of that study showed that thiopyran-4-one **112** undergoes highly diastereo- and enantioselective aldol reactions when catalyzed with (*S*)-proline[††]. Interestingly, when this protocol was applied to a more synthetically useful[‡‡] chiral aldehyde (±)-**119**, the reaction proceeds with dynamic kinetic resolution to afford a single diastereoisomer in 56% yield and >98% ee (Scheme 40).[170]

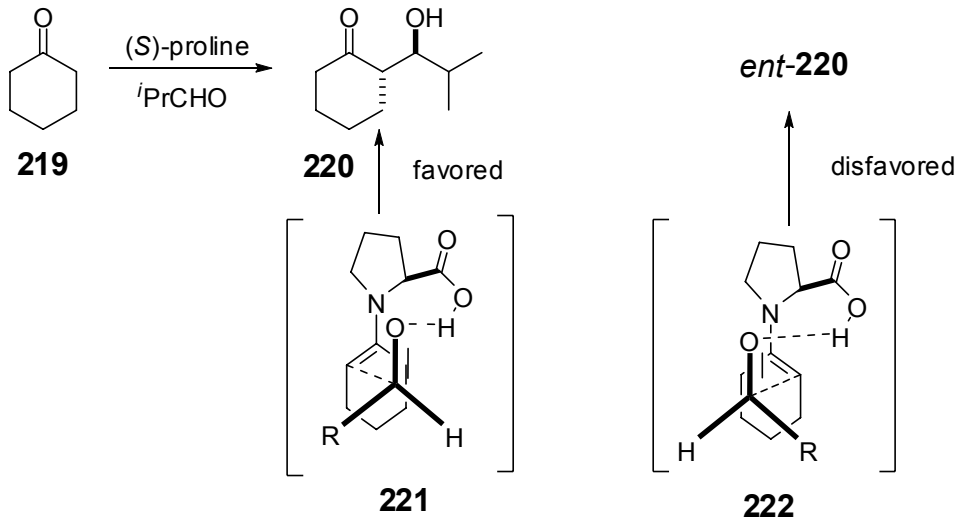
[††] A similar result was reported by Pihko and co workers.[169].

[‡‡] Aldol adducts from this reaction furnish tetrapropionate units after desulfurization.



Scheme 40: Proline catalyzed aldol reaction of (±)-**119** with thiopyran-4-one.

Mechanistic studies on both the intra- and intermolecular proline catalyzed direct aldol reaction have provided evidence of a carboxylic acid catalyzed addition of a proline enamine to the carbonyl groups.[171] Proposed transition state structures[172] (Scheme 41) for the intermolecular reaction suggest a preferential addition from the *re* face of the β–carbon in an *anti* oriented enamine to the *re* face of the aldehyde for the example given. The major difference in the alternative transition states proposed is in the greater stability of the *anti* oriented enamine **221** *vs* the *syn* **222**. As such the absolute configuration of the proline catalyst controls the face selectivity for the enamine addition and the face of the aldehyde attacked is controlled by the 'closed' transition state (i.e the steric influence of the R group).



Scheme 41: Proposed transition state models for proline catalyzed direct aldol addition.

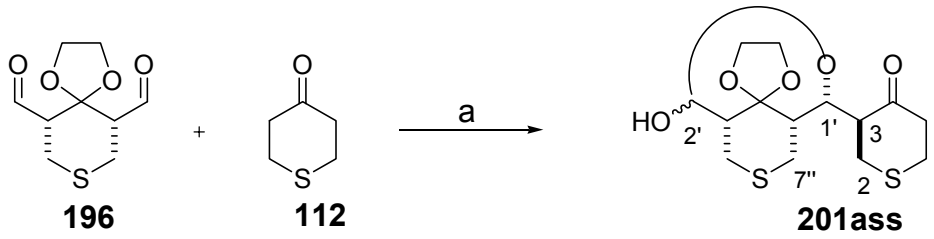
In a similar reaction with a chiral aldehyde, the intrinsic diastereoface selectivity of the aldehyde can either reinforce or counteract the face available for the addition as dictated in the closed transition state thus resulting in double diastereodifferentiation and/or kinetic resolution.

The aldehyde **119** has high 'Felkin' diastereoface selectivity and in an (*S*)-proline catalyzed reaction with **112** it is (*S*)-**119** that reinforces the selectivity of the preferred transition state. The 'matched' reaction of (*S*)-**119** with **112** gives a single stereoisomer (-)-**120as** (>98% ee). The reaction must occur with dynamic kinetic resolution since more than 50% yield of adduct **120as** was isolated and the aldehyde **119** was shown to undergo proline catalyzed isomerization under the reaction conditions.

The remarkable stereoselectivity observed in the reaction of **112** with **119** prompted an investigation into the use of proline as a chiral mediator for the desymmetrization of **196**.

2.5.2 Proline-catalyzed group selective aldol addition of thiopyranone 112 to *meso* dialdehyde 196

The proline-catalyzed direct aldol reaction addition of **112** with *meso* **196** under the previously established conditions[168] proceeded with good enantio- and diastereoselectivity to give **201ass** as the only aldol adduct in 68% yield and 92% ee (Scheme 42).[170] Adduct **201ass** was a 3:1 mixture of lactol anomers (in C_6D_6 solution) favouring the 2'*S* diastereoisomer.



Scheme 42: Proline catalyzed direct aldol reaction of **112** to **196**

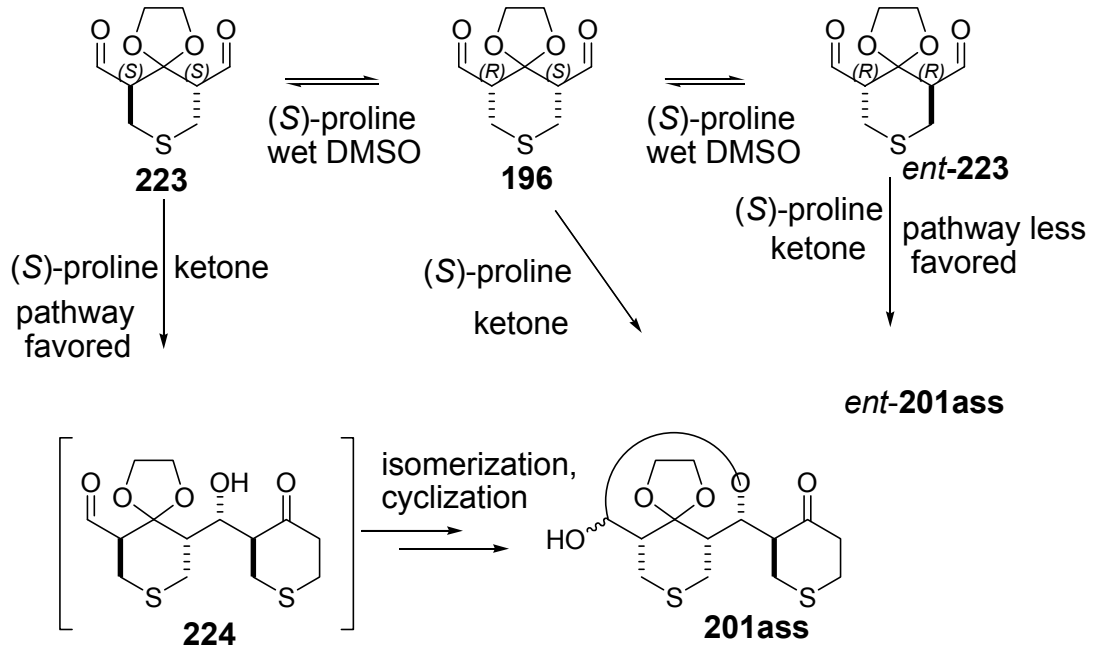
a) **196** (1M in DMSO), **112** (3 equiv.), H_2O (4 equiv.), (*S*)-proline (0.5 equiv), 2 days, r.t

Attempts to improve the yield of **201ass** by increasing the amount of **112**, the premixing time of **112** with proline, or the overall reaction time were not successful. Interestingly, the racemic **201ass** was obtained from the reaction of lithium enolate **118** with *meso* dialdehyde **196** (see section 2.4).

An observation made in the initial attempt to synthesize the *meso* dialdehyde **196** using standard Swern oxidation protocol,[106] indicates that **196** readily isomerizes to an inseparable mixture of the C_s and C_2 diastereoisomers. The stability of the hemiacetal **201ass** and the facile isomerization of **196** together suggested that the stereocenter α- to the hemiacetal group could be set under thermodynamic control. Isomerization of **196** under the aldol reaction conditions was shown to occur with a half life of 115 min[§§] to give a 3.5:1

[§§] See the appendix for the data and calculation.

equilibrium ratio of **223** and **196**, respectively. This suggests that the aldol adduct **201ass** could be formed via two different reaction pathways (Scheme 43).



Scheme 43: Proposed reaction pathways for the formation of **201ass**.

The first pathway involves a direct enantiotopic group selective addition to the (S)-aldehyde in *meso* **196** followed by cyclization. The second pathway proceeds via aldol addition to the (*S,S*)-**223** diastereoisomer followed by isomerization of the remaining aldehyde group and then cyclization. These pathways cannot be distinguished by my experiments. As expected, proline catalyzed aldol reaction of **112** with (±)-**223** or with an equilibrium mixture of (±)-**223** and **196** gave results similar to those obtained from the reaction with *meso* **196** (65% yield and 92%ee).

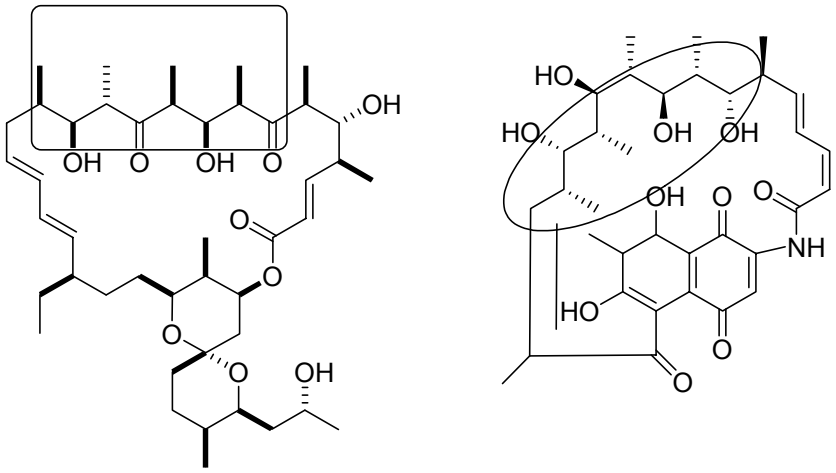
The selective formation of the aldol adduct **210ass** can be explained to be the result of preferential addition to the *re* face of the (*S*)-aldehyde group as dictated by the catalyst [(*S*)-proline] and the high Felkin diastereoface selectivity intrinsic to the thiopyran based ketal protected aldehyde.[22] The relative and

absolute configuration of the aldol adduct **201ass** is as shown and was determined by X-ray crystallography (see section 2.6 and appendix D).

The selective addition of the enolate to (*S,S*)-**223** combined with isomerization of (*R,R*)-**223** to produce more (*S,S*)-**223** is a dynamic kinetic resolution process. Similarly, the enantiotopic group selective addition to *meso*-**196** combined with isomerization of racemic **223** is a dynamic kinetic resolution process. In either case, the product **201ass** is obtained selectively because the rate of isomerization of the dialdehyde is faster than the rate of any competitive aldol reactions. The isomerization of the aldol adduct from (*S,S*)-**223** (i.e. **224**) to form **201ass** can be regarded as a thermodynamic resolution. Thus, the whole process may be viewed as an unusual combination of enantiotopic group selective reaction with a dynamic kinetic and thermodynamic resolution.

2.5.3 Derivatization of (3*S*)-Tetahydro-3-[(1*R*,2*RS*,4*R*,5*S*)-2-hydroxyl-spiro[3-oxa-7-thiabicyclo[3.3.1]nonane-9,2'-[1,3]dioxolane]-4-yl]-*H*-thiopyran-4-one (201ass) towards useful polypropionate fragments.

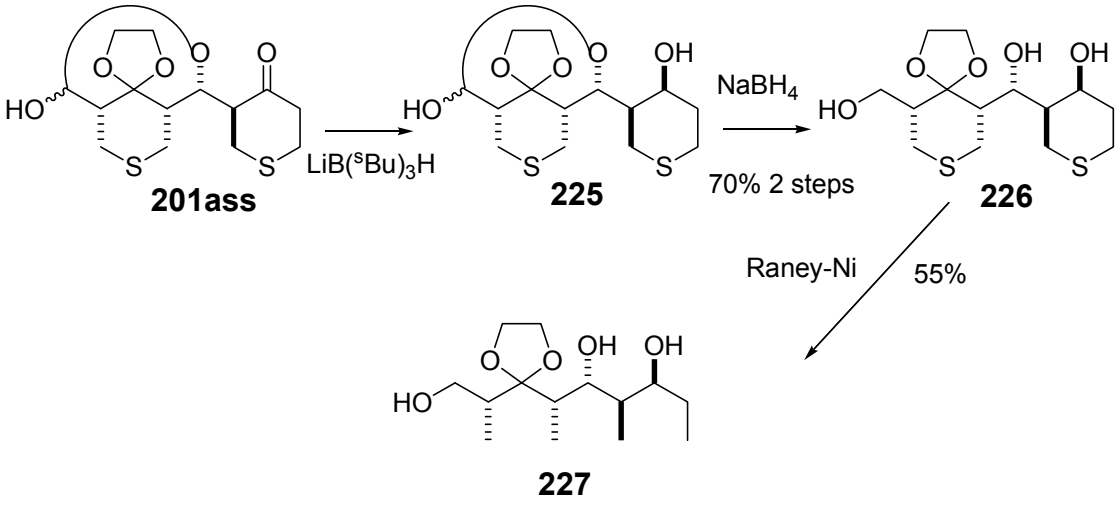
The aldol adduct **201ass** can be utilized in two ways: the first as a tetrapropionate fragment that could be applied in the total synthesis of natural products such as rutamycin B[50,173] and proansamycin X[174] (Figure 33) and secondly it can be re-functionalized to give an enriched aldehyde that can be coupled with another ketone unit to furnish an enriched hexapropionate synthon.



rutamycin B proansamycin X

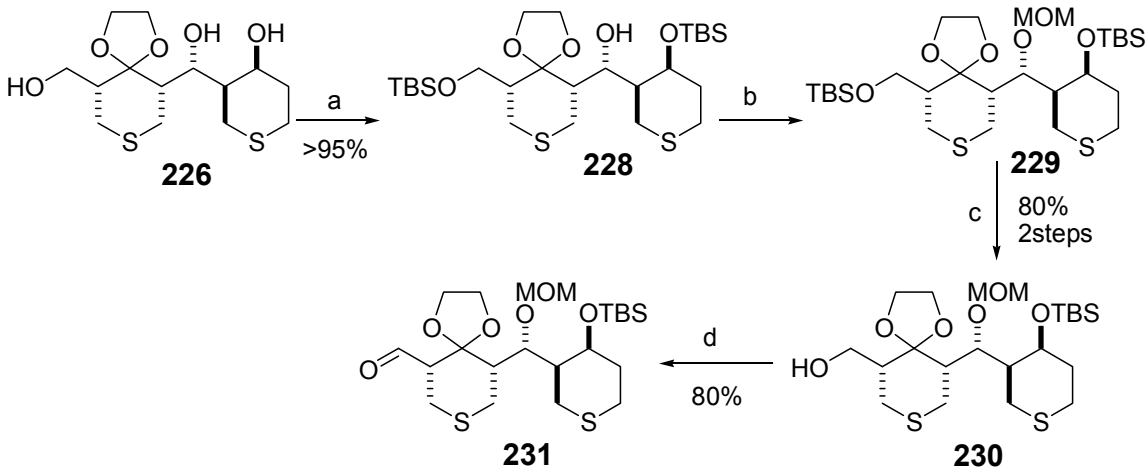
Figure 33: Examples of natural products containing tetrapropionate fragment that fits into adduct **201ass.**

Stereoselective reduction of the ketone group in **201ass** using L-selectride® followed by $NaBH_4$ reduction of the hemiacetal furnished the triol **226**. The desulfurization of the triol adduct was somewhat problematic and suspected redox products were detected in the crude reaction mixture[158] (Scheme 44). The low yield (55%) of **227** obtained from the desulfurization reaction is attributed to difficulties in quantitatively isolating the very polar product.



Scheme 44: Elaboration of **201ass** into a tetrapropionate fragment.

In order to convert the triol **226** into a suitable derivate for a second aldol coupling, the secondary alcohol groups need to be selectively protected prior to oxidation of the primary alcohol to an aldehyde. Attempts to protect the 1,3-diol in **226** as an acetonide were not successful. An attempt to fully protect the triol as the tris-TBS ether gave only the bis protected ether **228** despite extended reaction time, excess reagents, and high concentration. Protection of the secondary alcohol in **228** as the MOM ether followed by selective hydrolysis of the primary TBS ether yielded **230** in 73**%** over the 2 steps. Oxidation of the primary alcohol under modified Swern's protocol[106] gave the desired aldehyde **231** in 80% yield (Scheme 45).



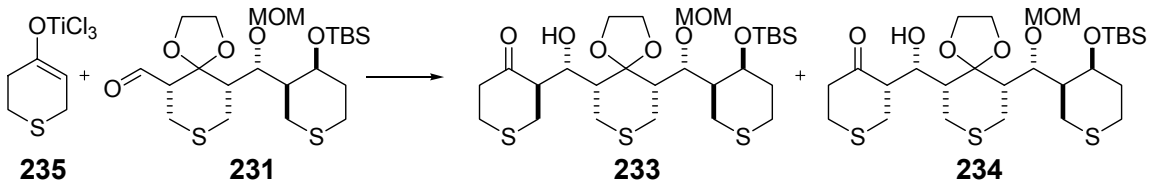
226 **228** **229** **230** **231**

a) 2 equiv TBSOTf, 4 equiv Et_3N, DCM, rt; b) 5 equiv MOMCl, 7.5 equiv DIEA, *n*Bu_4NI, DCM, rt; c) 10% aq HF, THF, rt; d) $(COCl)_2$, DMSO, DMS, DIEA

Scheme 45: Synthesis of aldehyde **231**

In a preliminary study, aldol reaction of aldehyde **231** with excess of the titanium enolate generated from **112** (i.e. **232**) gave a 1:1.2 ratio of **233**:**234** in 92% combined isolated yield (Scheme 46). Although the stereoselectivity of the reaction is poor, it is interesting to note that both adducts result from the 'Felkin' addition to the aldehyde.

Unfortunately, attempts to carry out an 'anti Felkin' addition to the aldehyde under Mukaiyama type conditions[114] mediated by $MgBr_2 \cdot Et_2O$ or Me_2AlCl were not successful as only the starting aldehyde was recovered as a mixture of diastereoisomers.



Scheme 46: Aldol reaction of **231** with thiopyranone **112.**

2.5.4 Summary and conclusions.

The enantiotopic aldehyde groups in the *meso* dialdehyde **196** were successfully differentiated in an aldol reaction catalyzed by proline. The unusually high stereoselectivity observed in the reaction is the result of the high facial bias imposed by (*S*)-proline, leading to only attack on the *re*-face of the aldehyde and also the high intrinsic Felkin diastereoselectivity in the β-ketal aldehyde. This reaction combines a dynamic kinetic resolution and a thermodynamic process to afford a single product in good yield and good ee. The faster rate of isomerization catalyzed by proline when compared to the aldol accounts for the dynamic kinetic resolution step, while the faster rate of cyclization when compared to the second aldol addition accounts for the dynamic thermodynamic resolution process. This process is particularly interesting in that the C_2 and *meso* dialdehydes or a mixture of the two gave the same product.

The aldol adduct was successfully converted to a tetrapropionate fragment that could be find applications in the syntheses of natural products. Conversion of the aldol adduct **201ass** to an aldehyde suitable for a second aldol coupling was also achieved. A second aldol coupling was carried out to give a mixture of 2 out of the 4 possible aldol adducts in high yield. These two enantioenriched hexapropionate building blocks might be used in natural product synthesis.

2.6 Stereochemical assignment of the aldol diastereoisomers and derivatives.

The assignment of the relative and absolute configurations of all the aldol adducts and their derivatives are discussed individually in subsections. Each subsection consists of products arising from the same aldol process.

2.6.1 Stereochemical assignment of aldol adducts and derivatives from 124.

The aldol products from the reaction of benzaldehyde with different enolates generated from **124** gave two aldol products **161as** and **161s.** Adduct **161as** was isolated as a crystalline compound while **161s** existed as an equilibrium mixture of three adducts. Similar reactions of enolates of **124** with **119** gave a mixture of products in which adduct **168** was isolated as a solid. The assignment of the relative configurations of these adducts and their derivatives are discussed individually in the following subsections.

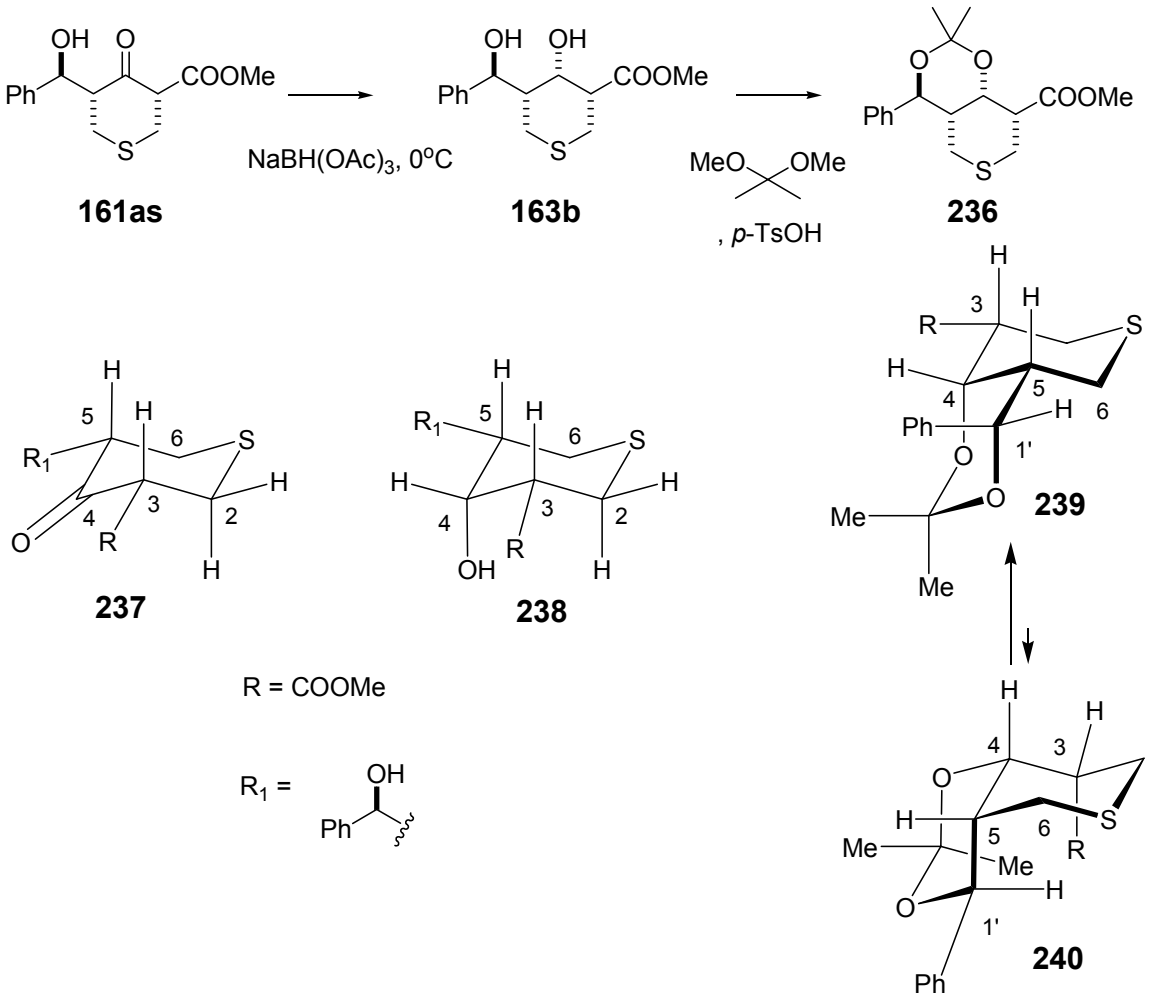
2.6.1.1 Assignment of relative configurations in 161as.

The relative configuration of the two substituents on the thiopyran ring in **161as** was assigned based on the large vicinal coupling constant between HC-3 and HC-2ax (12 Hz) and between HC-5 and HC-6ax (12 Hz), indicating that the two substituents are equatorial.

The relative configuration between HC-1' and HC-5 in **161as** was assigned from the analysis of the ^{1}H NMR of the acetonide derivative prepared according to Scheme 47. Hydroxyl directed stereoselective reduction[145] of the ketone group in **161as** gave the diol adduct **163b** as the only product (see

section 2.3.3.1) which was subsequently transformed into the acetonide **236** by treatment with 2,2-dimethoxypropane and catalytic *p*-TsOH.

Considering the ring system of the diol adduct **163b**, the small vicinal coupling constant between HC-4 and HC-5 (2 Hz) and between HC-4 and HC-3 (1.5 Hz) indicates that the hydroxyl group is in the axial position on the ring assuming no isomerization at the α–position to the ester group.



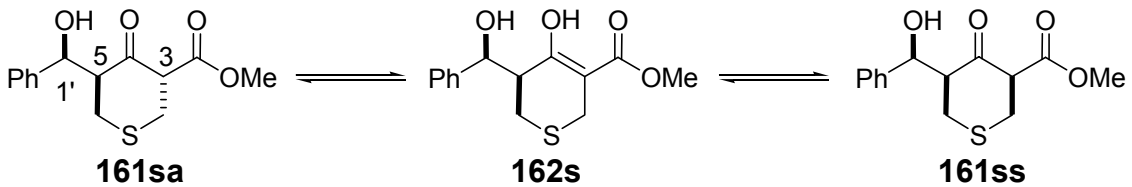
Scheme 47: Structure determination of aldol **161as**

Analysis of the ^{13}C NMR of the acetonide **236** reveals a chemical shift of 101.9 ppm for the C-3'' and 23.6 ppm and 25.2 ppm for the 2 methyl groups of

the acetonide. These chemical shifts indicate a 1,3-*anti* diol[146,147] relationship for the alcohol groups confirming the result expected from the hydroxyl-directed reduction. The HC-4, HC-5-*syn* relationship and the HC-4, HC-1'-*anti* relationship determined as above indicate that the relative configuration between HC-5 and HC-1' is *anti*. Analysis of the ^{1}H NMR of the acetonide **236** reveals a coupling constant of 6 Hz for HC-1' suggesting a *cis*-fused tetrahydrothiopyran[4,3-d]-1,3-dioxin ring system thus confirming the HC-1',HC-5-*anti*-HC-5,HC-3-*cis* relative configuration for the aldol adduct **161as**.

2.6.1.2 Partial assignment of relative configurations in 162s, 162sa and 162ss.

The structure of the aldol adducts **162s, 162sa and 162ss** could not be unambiguously assigned due to the fact that they exist as an equilibrium mixture (Figure 34). The relative configuration between HC-5 and HC-1' for all three isomeric adducts are assigned as *syn* based on the small vicinal coupling constants (2, 3 and 3.5 Hz) observed for HC-1'. This relative configuration is confidently assigned because the only other adduct (**161as**) from the reaction that gave **162s, 162sa and 162ss** is unequivocally assigned as the HC-1',5-*anti* adduct.

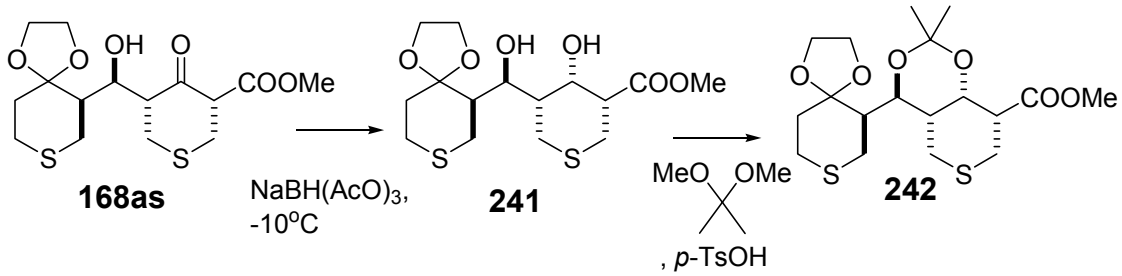


161sa **162s** **161ss**

Figure 34: Equilibrium mixture of the keto and enol forms of syn aldol adduct **161s.**

2.6.1.3 Assignment of relative configurations in 168.

The relative configurations in the stable aldol adduct **168** isolated from the reaction of lithium dienolate **160a** and aldehyde **119** was assigned following the same sequence that was used for **161as**. Stereoselective reduction of **168as** at -10 ^{o}C gave a 14:1 ratio of two in separable diols (the reaction was found to be less selective at high temperature, 1:1 at r.t and 6:1 at 0 ^{o}C). Treatment of the mixture of diols with 2,2-dimethoxypropane in the presence of catalytic *p*-TsOH afforded the acetonide **242** as the major product (Scheme 48).



Scheme 48: Structure determination of aldol **168as**

Analysis of the ^{1}H NMR spectrum of **168as** reveals that the two substituents on the thiopyran ring are in equatorial orientations as indicated by the large vicinal coupling constants in between HC-2 and HC-3 and between HC-6 and HC-5 (12 Hz).

Analysis of the ^{13}C NMR spectrum of the acetonide **242** reveals a chemical shift of 101.7 ppm for C-5'' and 24.5 ppm and 25.2 ppm for the 2 methyl groups of the acetonide. These chemical shifts indicate a 1,3-*anti* diol[146,147] relationship for the alcohol groups confirming the result expected from the hydroxyl directed reduction. The HC-4, HC-5-*syn* relationship and the HC-4, HC-1'-*anti* relationship determined as above indicate that the relative configuration between HC-5 and HC-1' is *anti*. The relative configuration between HC-1' and HC-6'' is assigned as shown based on assumption of high 'Felkin' diastereoface selectivity in addition to aldehyde **119**.[22]

2.6.2 Stereochemical assignment of the aldol adducts and derivatives from (*Z*)-tetrahydro-3-(methoxymethylene)thiopyran-4-one (157).

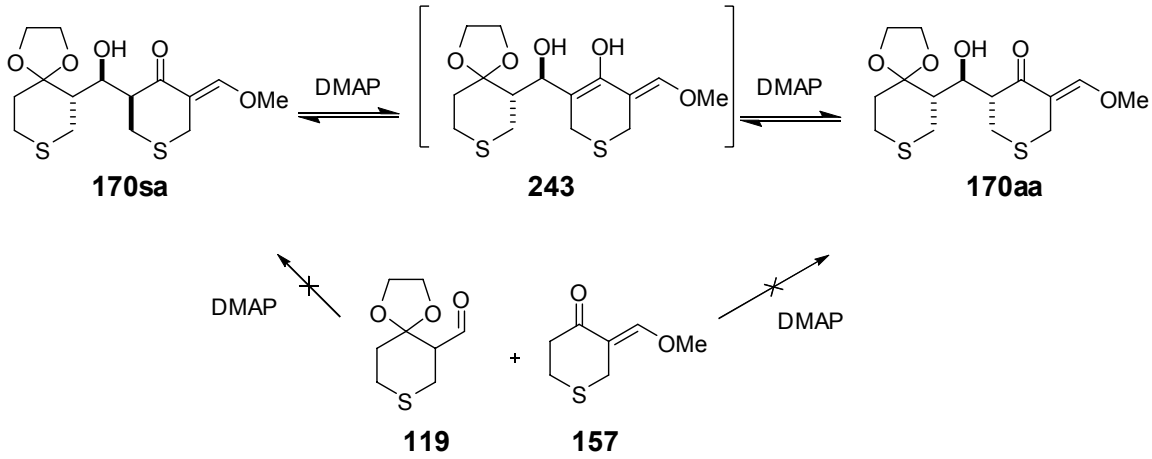
The relative configurations in the four aldol adducts obtained from the reactions of **119** with **157** and/or **158** were determined indirectly from their derivatives. In the course of the study to hydrolyze the methoxy protecting group from the aldol adducts **170**, MOM protected derivatives were prepared and one of the products was fortunately crystalline. Reduction of the aldol adducts **170** also gave diol adducts of which two were obtained as single crystals. This allowed the relative configurations in these adducts to be determined by X-ray crystallography. The individual aldol adducts **170** are discussed in the following subsections.

2.6.2.1 Assignment of relative configurations in 170sa and 170aa

X-ray analysis (See appendix A) of the MOM derivative of **170sa** (**190sa**) confirms the indicated of 1',6''-*anti* and 1',3-*syn* relative configuration as expected from the $MgBr_2$▪Et_2O mediated reaction.[22] Only two products (**170sa** and **170aa**) were detected from this reaction and the propensity of the aldehyde **119** to give 'anti-Felkin' aldol products under these conditions strongly suggested that the other product from the reaction (**170aa**) will have an *anti-anti* relative configuration. To confirm this prediction, isomerization of **170aa** by enolization[175,176] was carried out in $CDCl_3$ using DMAP[***] (0.4M) to obtain a 1:2.2 equilibrium ratio of (**170aa**:**170sa**) within 24h (the ratio stays the same over 7 days). A similar experiment starting with **170sa** gave the same result (Scheme 49). The fact that no aldol product was detected from **119** and **157** in the

[***] Attempts to isomerize **170** with imidazole[175.176.] resulted in decomposition of the aldol adduct.

presence of DMAP under these reaction condition, rules out the equilibration of **170aa** and **170sa** via a retroaldol-aldol mechanism. It is noteworthy that neither elimination nor retroaldol products were detected under these conditions.



Scheme 49: Isomerization of aldol adducts via enolization.

2.6.2.2 Assignment of relative configurations in 170sa and 170aa

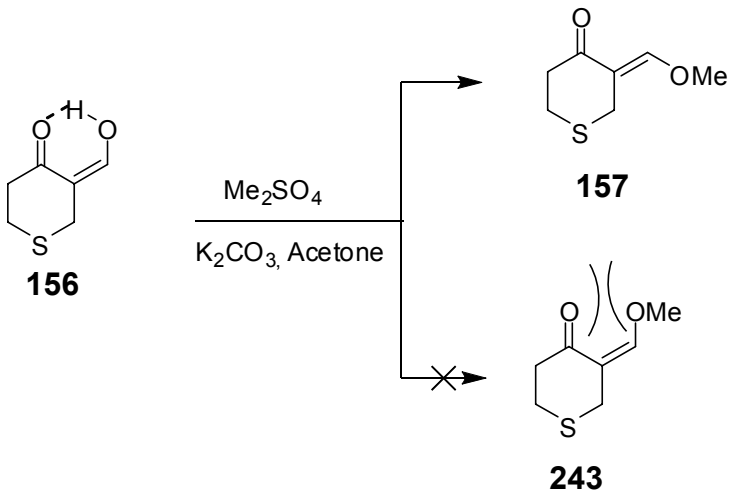
Reduction of the aldol adducts **170ss** and **170as** (see section 2.3.5.1) gave the crystalline diols adducts **182** and **181aas,** respectively. X-ray crystallographic analysis (See appendix B and C) of **182** and **181aas** confirmed the relative configurations to be 1',6''-*syn*-1',3-*syn* in **170ss** and 1',6''-*syn*-1',3-*anti* for **170as**. Both aldol adducts result from 'Felkin' addition to the aldehyde **119** as expected for the reaction conditions under which these adducts were prepared.[22] Subjecting **170ss** to the isomerization conditions established for **170aa** and **170sa**, gave a 2.5:1 equilibrium ratio of **170ss**:**170as** within 24 h (the ratio stays the same over 7 days). A similar result was obtained starting from **170as**, confirming that equilibrium was attained. The fact that the isomerization of **170ss** gave only **170as** with both structures confirmed by x-ray crystallography, gives further proof to the structure assigned to **170aa**.

An interesting observation that is worth mentioning in this section was made when the aldol adducts **170as** and **170ss** were isolated from crude reaction

mixtures. FCC using deactivated silica gel (5% V/W, Et_3N/ silica gel) to prevent retroaldol and elimination was found to be counterproductive as rapid isomerization of the aldol adducts occurred within the time frame of elution. FCC of a 9:1 ratio of **170as**:**170ss** on deactivated silica gel (1/4 V/V→ 1:1 V/V, EtOAc/ hexanes) gave a 1.4:1 ratio of the aldol adducts within 1 h without detection of any elimination products. Although this process is counterproductive in the context of isolation for either of the aldol adducts, it may constitute an alternative and cheaper approach to isomerising aldol adducts. The generality of this observation will need to be investigated.

2.6.2.3 Assignment of the geometry of the enol in 157 and 158.

Attempts to determine the geometry of the olefin in compounds **157** and **158** via NMR (NOE) did not give conclusive results. It is safe to assume that the *Z* geometry found in the aldol adducts **170** reflects the geometry in the starting material **157**. This geometry should be more favoured due to less dipole-dipole interaction between the oxygens of the methoxy group and the ketone (Scheme 50). The inter-conversion of the *E* geometry in **157** to the *Z* in **158** under basic conditions is not totally surprising and has precedence in the literature.[177]



Scheme 50: protection of the enol ketone **156** to make **157**

2.6.3 Stereochemical assignment of the aldol adducts from the the reaction of 196 with 121.

As discussed in section 2.4.3, three aldol adducts were isolated from the reaction of **196** with the boron enolate **121**. One of the adducts (**201ass**) which exits as a mixture of anomers is a product of mono addition to the dialdehyde **196**. The other two products are from double addition to the dialdehyde. Out of these two, one is symmetrical indicating a *meso* or C_2 symmetric compound while the other is non-symmetrical. Assignment of the relative configurations in these three aldol adducts is discussed individually in the following subsections.

2.6.3.1 Assignment of relative configurations in 201ass.

The structure of the mono addition product **201ass** was easily solved even though the compound is a mixture of two isomers and the ^{1}H NMR is somewhat complicated. Crystallization of **201ass** from benzene gave a crystal containing 9:1 ratio of the two anomers in the crystal lattice and the structure

was solved by X-ray crystallography (appendix E). The structure of the aldol adduct **201ass** is as expected from thiopyran boron enolate **121** addition to the ketal aldehyde **119** (i.e. anti aldol with Felkin addition).[22]

2.6.3.2 Assignment of relative configurations in 202as.

The ^{13}C NMR of **202as** shows only 11 signals indicating that the compound is symmetrical and as such *meso*. If it were to be a *C*2 symmetrical adduct, there would be 10 signals because the acetal carbons would be degenerate. Comparison of the ^{13}C NMR chemical shifts for of **202as** with those of the related carbons in the known aldols **120a-d** indicated that the structure of the major bis addition product **202as** is as shown in section 2.3.4 (See Figure 36 and Appendix F for the data in tabular form). The propensity of the aldehyde **119** to give the 'Felkin' addition products under the condition for the reaction further lends support to the assigned structure.

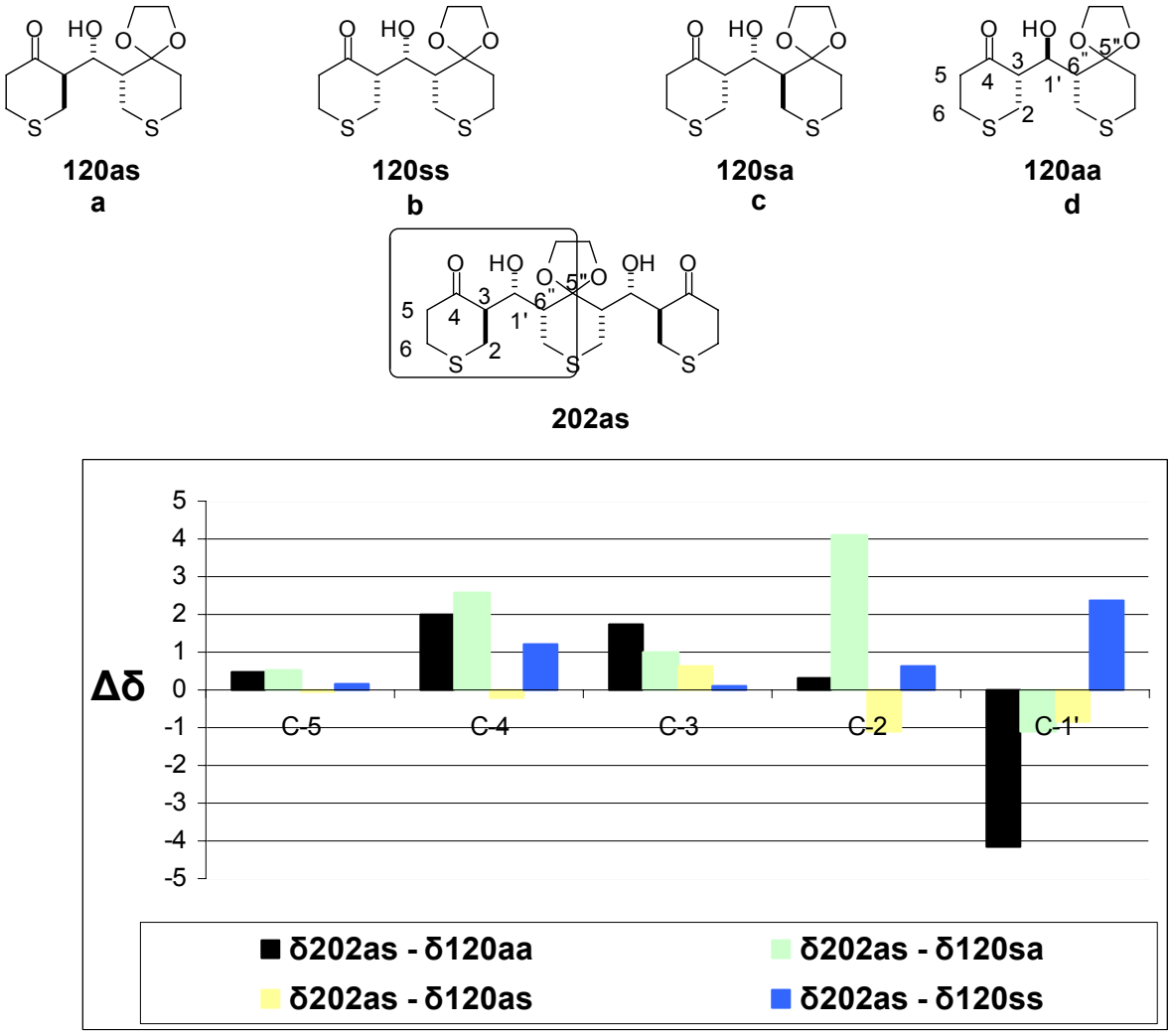
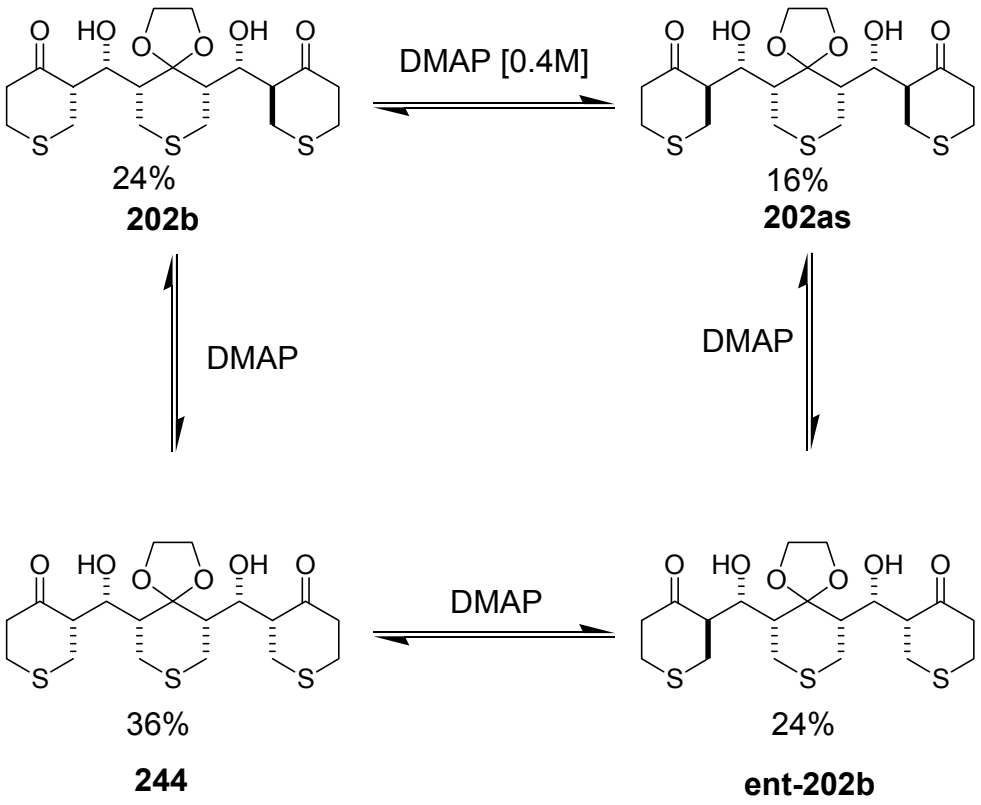


Figure 35: Comparison of ^{13}C NMR chemical shift differences of **202as** with **120a-d.**

2.6.3.3 Assignment of relative configurations in 202b.

The relative configuration in **202b** was assigned indirectly from isomerization of the adduct using DMAP in $CHCl_3$. ^{13}C NMR indicates that **202b** is a non-symmetrical bis addition adduct with 18 out of the 19 possible carbon having distinct signals in C_6D_6. The carbon signals for C7 and C9 are not resolved in C_6D_6. Isomerization of this chiral bis aldol adduct **202b** in the

presence of DMAP gave a 48:36:16 mixture of three stereoisomers (Scheme 49). ^{1}H NMR analyses of fractionations obtained by PTLC (EtOAc: Hexanes, 3:2 V/V) revealed that the major isomer was **202b** and that two the other isomers were *meso* adducts with the minor isomer identified as **202as** (Scheme 51). A similar result was obtained when **202as** was subjected to isomerization under the same condition.

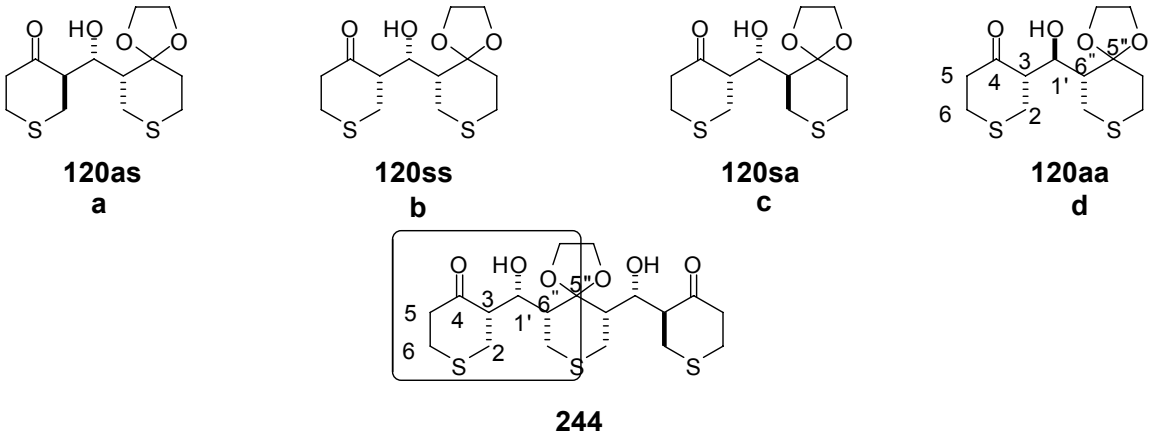


Scheme 51: Isomerization of chiral bis aldol **202b.**

The fact that the isomerization proceeds by enolization[175,176] and **202as** is one of the two adducts isolated from the process strongly suggest that the structures of **202as** and **202b** have the same relative configurations at the center not affected by enolization. The high propensity of the ketal protected aldehyde[22] for Felkin addition under the reaction conditions used for the preparation of the aldol adducts is consistent with the structure of **202b** which is

the only chiral Felkin addition adduct that could be formed from the reaction. Thus the second *meso*

aldol product **244** from the isomerization of **202b** and **202as** must be the all *syn* adduct. This is further supported by ^{13}C evidence from the comparison of related carbons with **120a-d** (Figure 36).



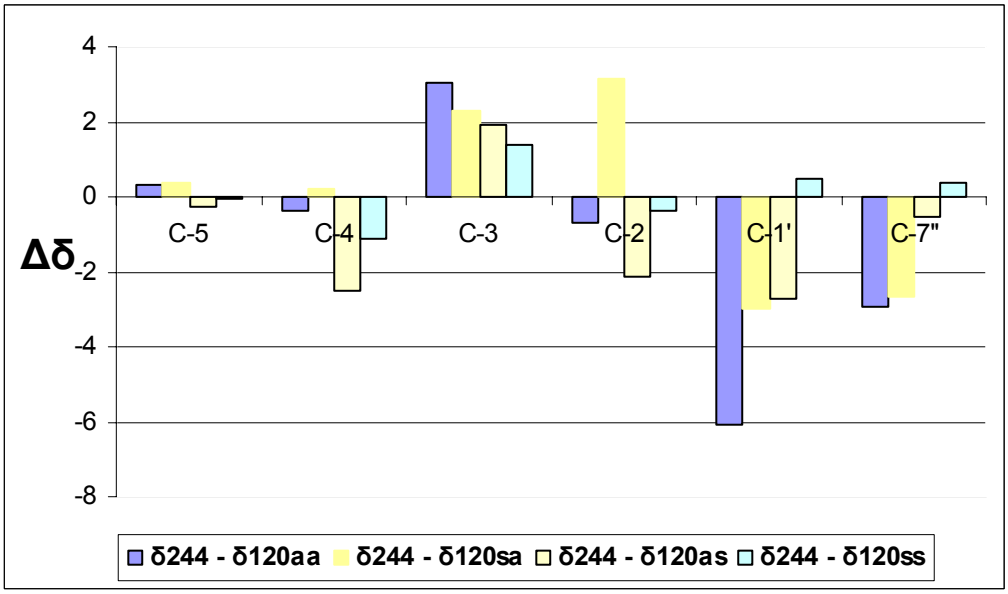


Figure 36: Comparison of ^{13}C NMR chemical shift differences of **244** with **120a-d**.

2.6.4 Stereochemical assignment of 201as and its derivatives.

The structure of the aldol adduct **201as** and the compounds derived from this adduct are discussed individually in the following subsections.

2.6.4.1 Assignment of relative configurations in 201as.

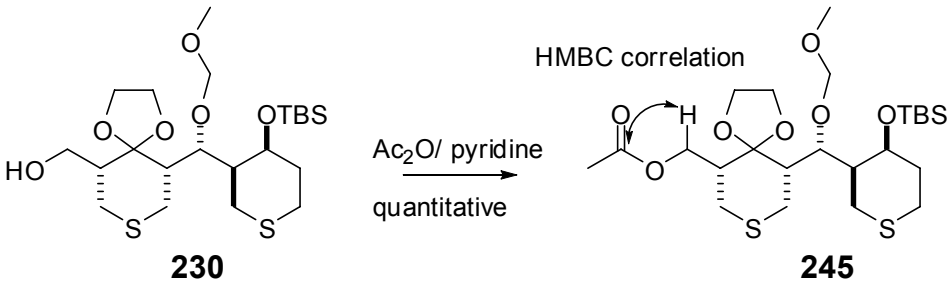
The structure of the enriched aldol adduct **201as** was assigned by comparison of the ^{1}H and ^{13}C NMR with that of the racemic **201as** obtained from the boron enolate (**121**) addition to the *meso* dialdehyde **196**. The spectra were identical.

2.6.4.2 Assignment of relative configurations in 226.

The structure of the triol **226** generated from the selective reduction of **201as** (a mixture of anomers) was assigned as shown. The new stereogenic center generated at C-4 was assigned based on the small vicinal coupling constants for HC-4 (2, 2, 5 Hz) suggesting an equatorial orientation for the hydrogen consistent with the expected equatorial attack on the ketone by the bulky reducing reagent. Additionally, both the relative and absolute configuration of the triol **226** were assigned by X-ray crystallography (see appendix E).

2.6.4.3 Assignment of the position of the TBS group in 230.

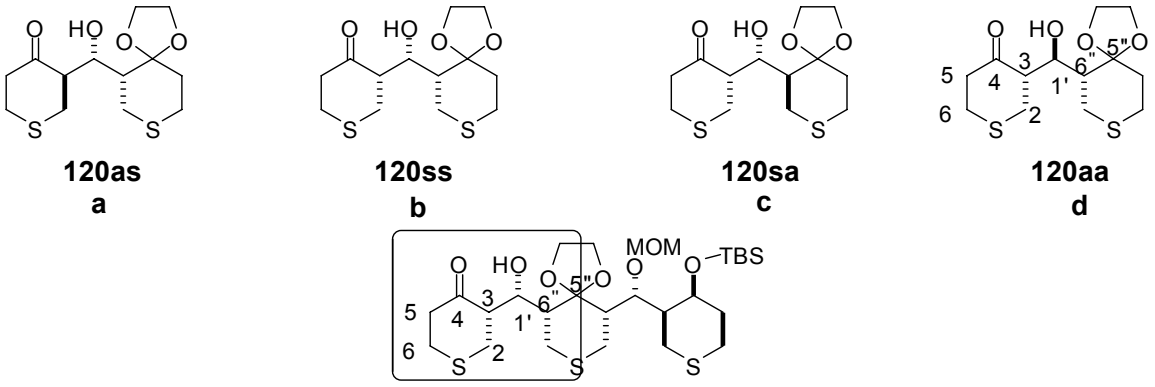
The position of the TBS ether in compound **230** was confirmed by analysis of the HMBC spectrum of the derived acetate **245**. The long range H-C correlation between the carbonyl carbon of the acetate and HC-2' confirms that the HC-1' hydroxyl group was not protected in the TBS protection of the triol (Scheme 52).



Scheme 52: Acetyl protection to confirm position of the TBS ether in **230**

2.6.4.4 Assignment of the relative configuration in the aldol adducts 233 and 234.

Two new stereocenters were generated in the aldol reaction of the titanium enolate **235** with **231** assuming no isomerization occurred at the aldehyde stereocenter. Comparison of ^{13}C NMR chemical shift difference of the "left" side of compound **234** with known aldol adducts **120a-d** suggests the relative configuration to be 1',6-syn-1',3'-syn (Figure 37 and appendix G for the data in a tabular form).



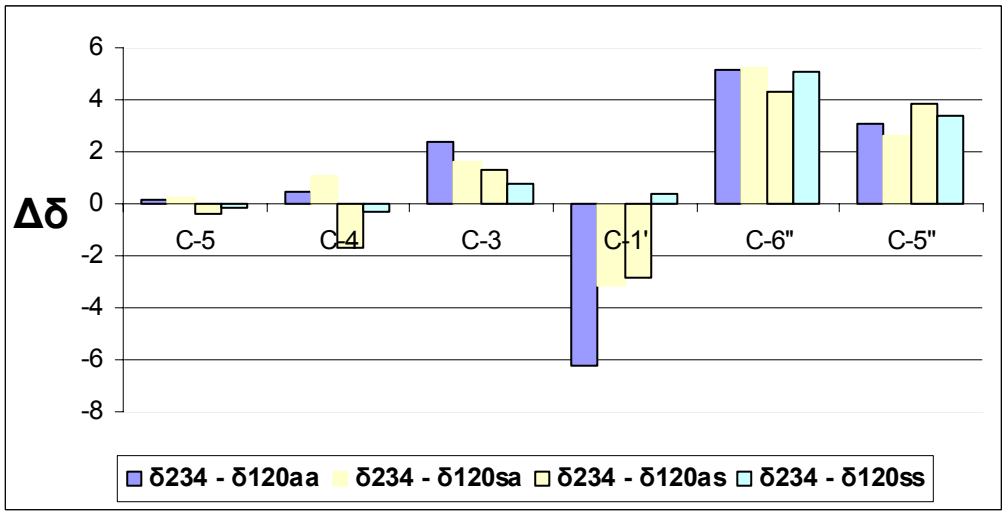
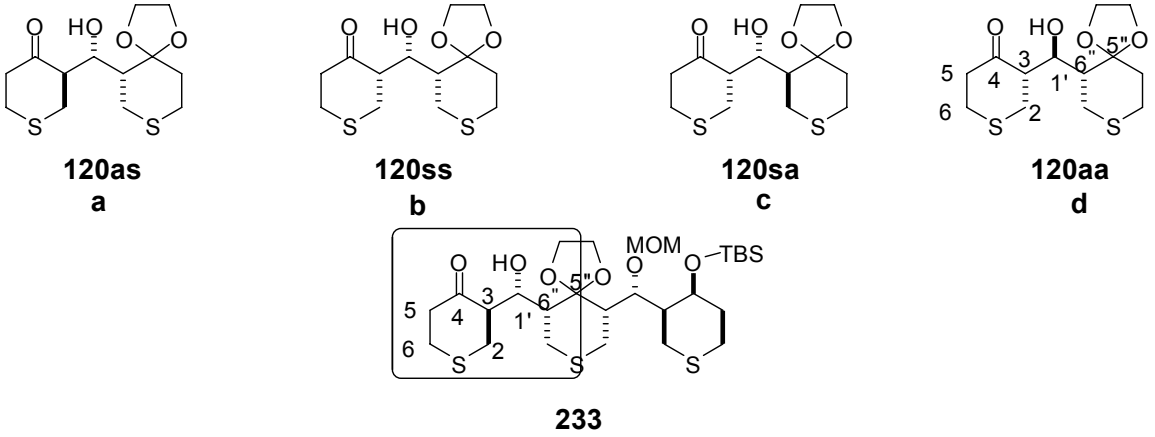


Figure 37: Comparison of ^{13}C NMR chemical shift differences of **234** with **120a-d.**

Applying the same process to **233** confirms the relative configuration of the "left" side of the molecule to be 1',6-syn-1',3'-anti (Figure 38 and Appendix H for the data in a table form). These two products (**233** and **234**) would result from the expected[22] 'Felkin' addition to the aldehyde **231.**



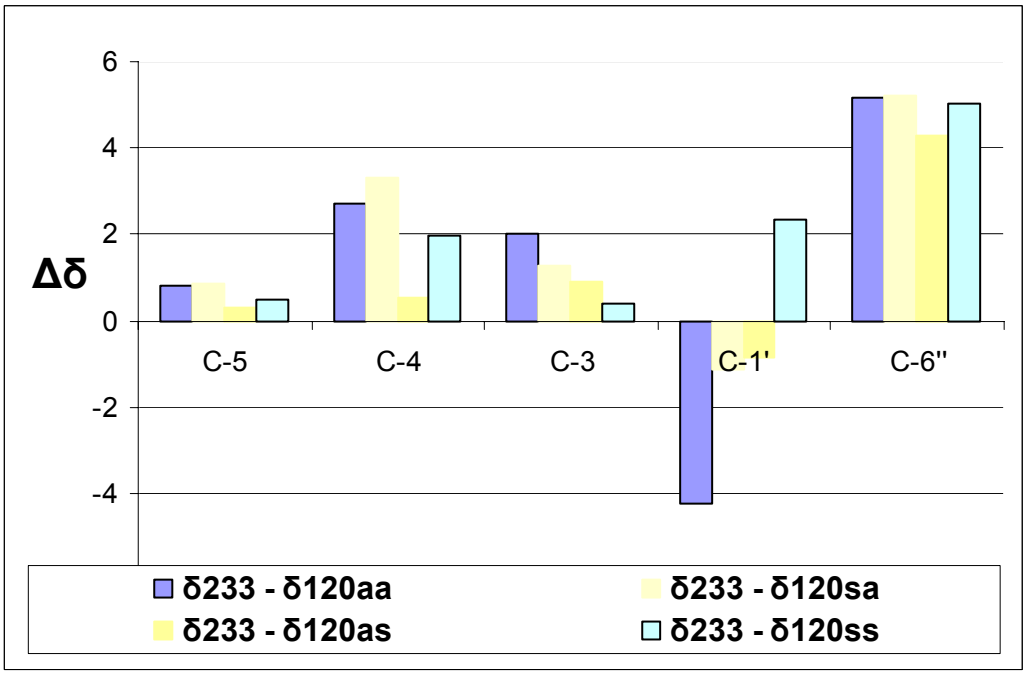


Figure 38: Comparison of ^{13}C NMR chemical shift differences of **233** with **120a-d.**

2.7 Application towards the synthesis of enteridic acid.

2.7.1 Introduction

Enteridic acid is a polypropionate natural product isolated by Řezanka and co-workers[9] as it's deoxy sugar esters enteridinine A and B from the slime mold *Enteridium lycoperdon* (Figure 39). A 30.5 g of sample lypophilized slime mold gave 17.1 mg of enteridinne A and 14.6 mg of B after extraction with *n*-BuOH, separation on a sephadex LH-20 column, and purification on reverse phase-HPLC.

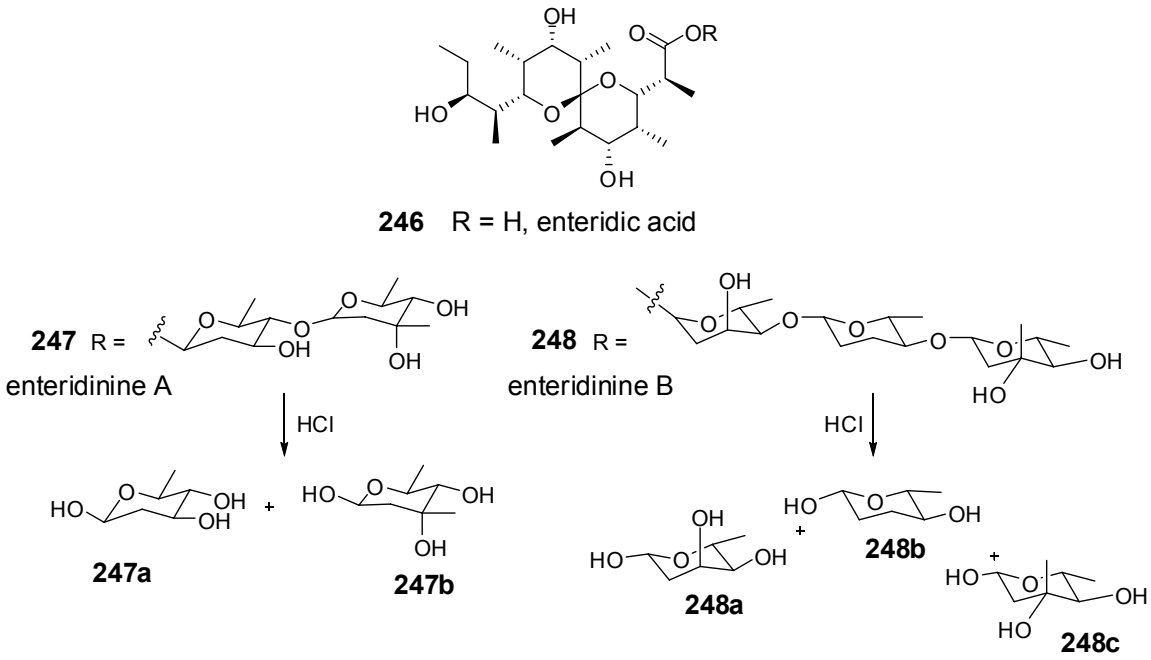


Figure 39: enteridic acid A and B

Alkaline hydrolysis of 14.2 mg of enteridinine B using 1 M NH_4OH in a sealed tube at 60 ^oC for 24 h gave 8.1 mg of the enteridic acid after neutralization to pH 7 with acetic acid. The mass obtained translates to 112% yield of enteridic acid which indicates that there is a problem with the result reported.

In line with Řezanka group's investigation into bioactive natural products, enteridinine A (**2**) and B (**2a**) were tested for activity against some bacteria and fungi. Enteridinine A (**2**) was found to inhibit the growth of Gram-positive bacteria while showing less activity to Gram-negative and some fungi (Table 13). Although enteridinine B did show less antibacterial activity when compared to enteridinine A, it has a 4-fold antifungal activity. The difference in bioactivity of these two closely related compounds was attributed to the cell permeability as modulated by the different sugar appendage.

Table 13: Antibacterial and antifungal activity of enteridinine A and B

Test organism*	enteridinine A(**247**)	enteridinine B(**248**)
Staphylococcus aureus	28	10
Bacillus subtilis	34	11
Escherichia coil	6	5
Saccharomyces cerevisiae	9	41
Candida albicans	3	12

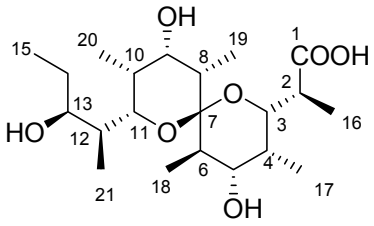
* Samples (10 µg) were applied to a 6.35 mm paper disks, and values are diameter (mm) of inhibitory zones

2.7.2 Structural elucidation

The structures of enteridinine A and B were assigned based on NMR spectroscopy (^{1}H, ^{13}C, COSY, NOESY, and HMBC data), UV, IR, mass spectroscopy and partial chemical degradation work.

Subjecting enteridinine A (**2**) to acid hydrolysis furnished two monosaccharides **247a** and **247b**, whose structures were confirmed by comparing their NMR spectral data and [α] to literature values, and the carboxylic acid **246**. A similar hydrolysis of enteridinine B gave three monosaccharides (**248a**, **248b** and **248c**) and the same carboxylic acid **246**. Analysis of the ^{1}H and ^{13}C NMR data of the carboxylic acid **246** indicated[9] the presence of six methyl, one ethyl, three oxymethine and one carbonyl group (Table 14).

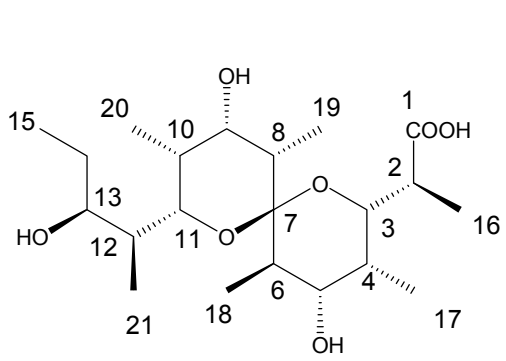
Table 14: Řezanka's reported data for enteridic acid.



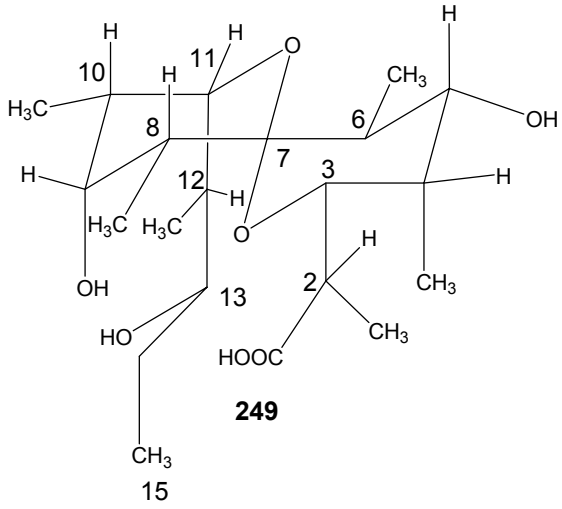
^{13}C #	^{1}H	J value	^{13}C
1	-		179.3
2	2.56 (1H)	6.7, 6.2	42.1
3	3.80 (1H)	6.2, 3.6, 1.2	66.9
4	1.75 (1H)	6.9, 4.5, 3.6	31.7
5	4.07 (1H)	10.5, 4.5, 1.2	74.5
6	1.65 (1H)	10.5, 7.0, 0.9	37.4
7	-	-	97.6
8	1.58 (1H)	7.0, 3.8, 1.4, 0.9	38.1
9	3.61 (1H)	4.5, 3.8, 1.2	72.8
10	1.94 (1H)	6.9, 4.5, 3.6, 2.1, 1.4	33.8
11	3.86 (1H)	7.6, 3.6, 1.2	69.0
12	2.04 (1H)	7.0, 7.6, 4.4, 2.1	38.4
13	3.41 (1H)	8.8, 4.4, 3.6	72.6
14	1.54 (1H)	14.6, 7.3, 3.6	14.8
14	1.54 (1H)	14.6, 8.8, 7.3	29.1
15	0.87 (3H)	7.3	10.1
16	1.19 (3H)	6.7	10.3
17	0.96 (3H)	6.9	11.4
18	1.06 (3H)	7.0	11.9
19	1.07 (3H)	7.0	12.4
20	0.93 (3H)	7.9	8.3
21	0.87 (3H)	7.0	9.1

The signal at δ 97.6 in the ^{13}C NMR spectrum of **246** indicated the presence of an acetal group and was supported by the IR data that showed two strong signals at 1175 and 1040 cm^{-1} typical of C-O-C bond. The ^{1}H-^{1}H COSY spectrum for **246** was used to construct two partial structures which were connected via HMBC and mass spectroscopic data to give the proposed spiroacetal structure.

A combination of vicinal ^{1}H-^{1}H coupling constants ($J_{3,4}$=3.6 Hz, $J_{4,5}$=4.5 Hz, and $J_{5,6}$=10.5 Hz) and NOE correlations indicated to the authors that one tetrahydropyran ring existed in a chair conformation with the substituents at C3, C4, C5, and C6 in equatorial, axial, equatorial, and equatorial orientations, respectively. The second tetrahydropyran ring was assigned to be in a chair conformation with the substituents at C8, C9, C10, and C11 in equatorial, axial, equatorial, and axial orientations, respectively, based on small vicinal coupling constants among H8-11, a long range and $^{4}J_{9,11}$ = 1.2 Hz, and NOE correlations between H8 and H10 (Figure 40). NOE correlations between H3/H8 and H6/H12 were used to assign the configuration at the spiro center. The absolute configuration at C2 was assigned as *S* from the ^{1}H NMR of the PGME esters (2-phenylglycine methyl ester) according to the method reported by Nagai and Kusumi,[178] while the relative configuration at C13 was assigned from the small coupling constant ($J_{12,13}$ = 4.4 Hz) between H12 and H13.



246

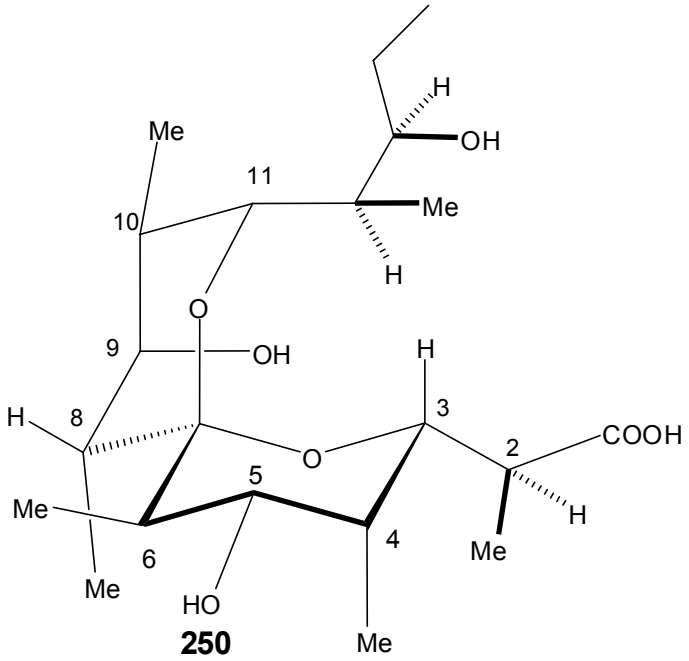


249

Figure 40: The structure for enteridic acid proposed by Rezanka *et al*. (as depicted in ref 9)

There are significant weaknesses in the arguments used to assign the structure of enteridic acid that put into doubt the proposed structure. Note that the 2D and 3D representation reported by Řezanka (Figure 40) do not share the same relative or absolute configuration. The relative configuration between C2 and C3 was assigned on the basis of a 6 Hz coupling constant ($J_{2,3}$ = 6 Hz) without any comment on the conformational analysis of the freely rotating C2-C3 bond required to substantiate that conclusion. Similarly, the basis for the assignment of the C11, C12, C13 relative configuration is not sufficiently substantiated. The uncertainty regarding the relative configuration between C2 and C3 puts in doubt the absolute configuration proposed for enteridic acid.

A 3D representation of my best guess of the the author's proposed structure for enteridic acid (Figure 41) shows that H3 and H8 are pointing away from one another which makes it difficult to rationalize the reported NOE correlation between them. This correlation was the basis for the author's assignment of the configuration at C7 (Figure 41).



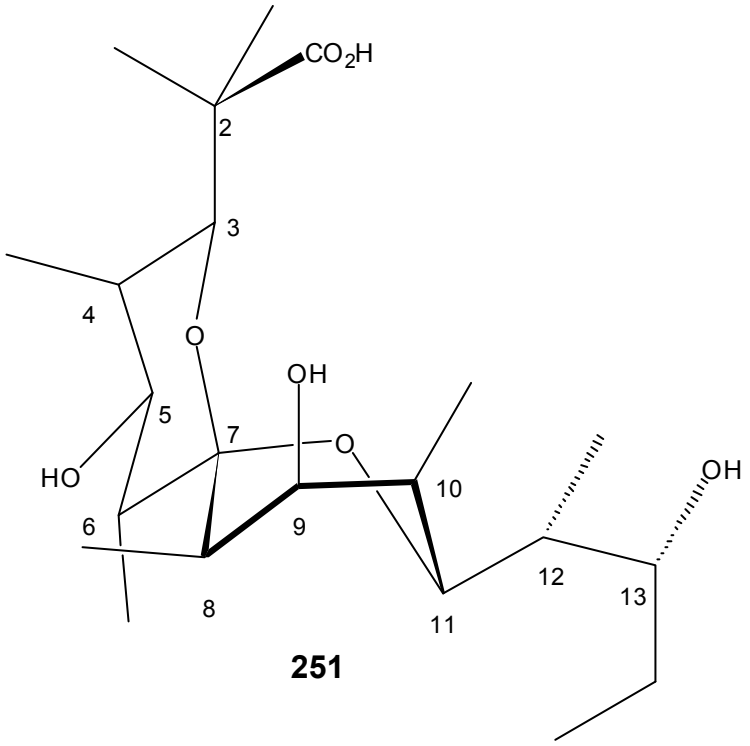
250

Figure 41: My 3D representation of Řezanka's proposed structure for enteridic acid.

2.7.2.1 Towards the determination of the core spiroketal fragment of enteridic acid

Conformational analysis of **250** using Spartan'04 (MMFF)[†††] indicated that conformer **251** was lowest in energy (relative energy of 17.99 kcal mol^{-1}). Interestingly, this conformer has one of the pyran rings in a boat conformation. Although the ^{1}H-^{1}H coupling constant data reported by the authors is consistent with conformer **251**, the NOE data reported does not match (Figure 42).

[†††] Conformational search done by Mr. Martin Gillis.



251

Figure 42: Predicted lowest energy conformer of the proposed structure by Rezanka.

Conformational anaylsis of various alternative stereoisomers of **250** was performed in an effort to find structures consistent with the reported data. According to Spartan, structure **253** represents the most stable conformer (relative energy of 17.86 kcal mol^{-1}) of one diasteroisomer of **250** (Figure 43). The difference between this stereoisomer and the one proposed by the authors is in the configuration at the spiro center. Structure **253** is consistent with both the ^{1}H-^{1}H coupling constants and the NOE correlation reported.

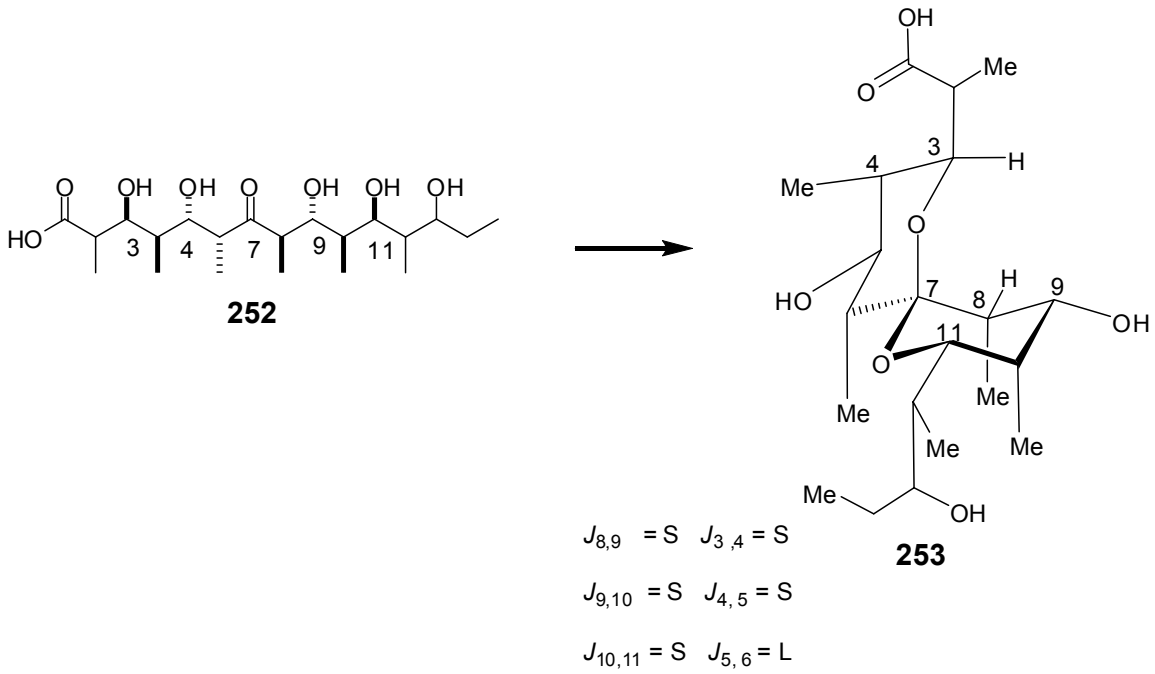


Figure 43: A proposed alternative structure for enteridic acid that fits the reported data.

As a means of validating the results of the conformational analyses described above, a series of spiroketal adducts were prepared and their structures determined. The preparation, structure determination and the result of conformational search on the prepared spiroketal adducts is discussed in the following subsections.

2.7.3 Proposed thiopyran-based synthetic route to enteridic acid.

The uncertainties in the proposed structure of enteridic acid pose a formidable synthetic challenge. A flexible synthetic route is required that is easily adaptable to generate a library of stereoisomers to firmly establish the correct structure and for structure-activity relationship (SAR) studies. In keeping with the theme of this research, the *meso* bisaldol **205** was considered as a suitable starting point (Figure 44).

The *meso* bis aldol **205** can be rapidly constructed in 50% yield from the reaction of boron enolate **118** (M = $B(Chx)_2$) with the *meso* dialdehyde **196** (see section 2.4). Enantioselective enolization of a protected derivative **205** followed by reduction should furnish enantiopure **259**. Stereoselective aldol reaction of **259** with propanal can provide a variety of stereoisomers of **258** depending on the reaction conditions. Oxidation at C-3, carboxylation, and reduction of the resulting β–ketoester should give **257**. The stereocenter at C-2 should be controllable depending on the reduction conditions.

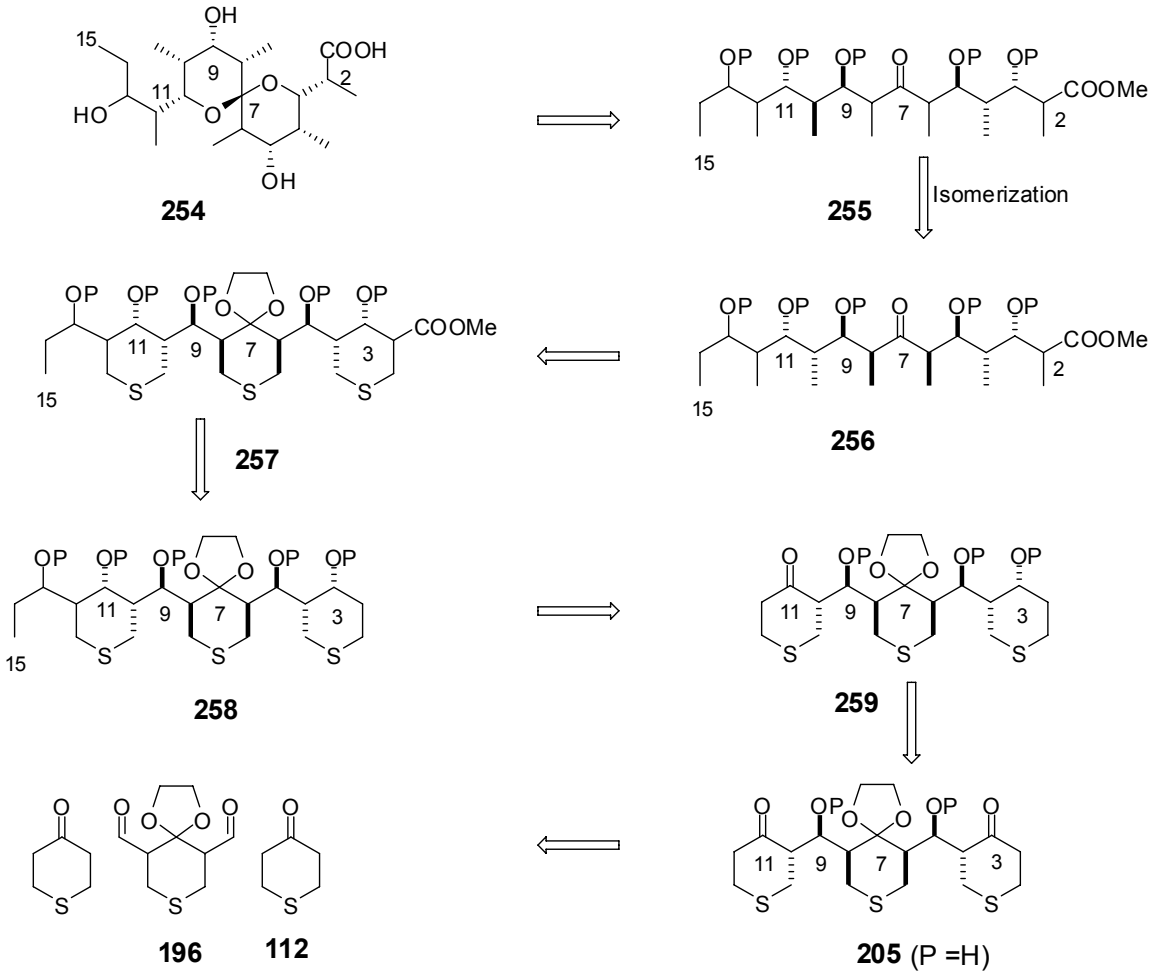


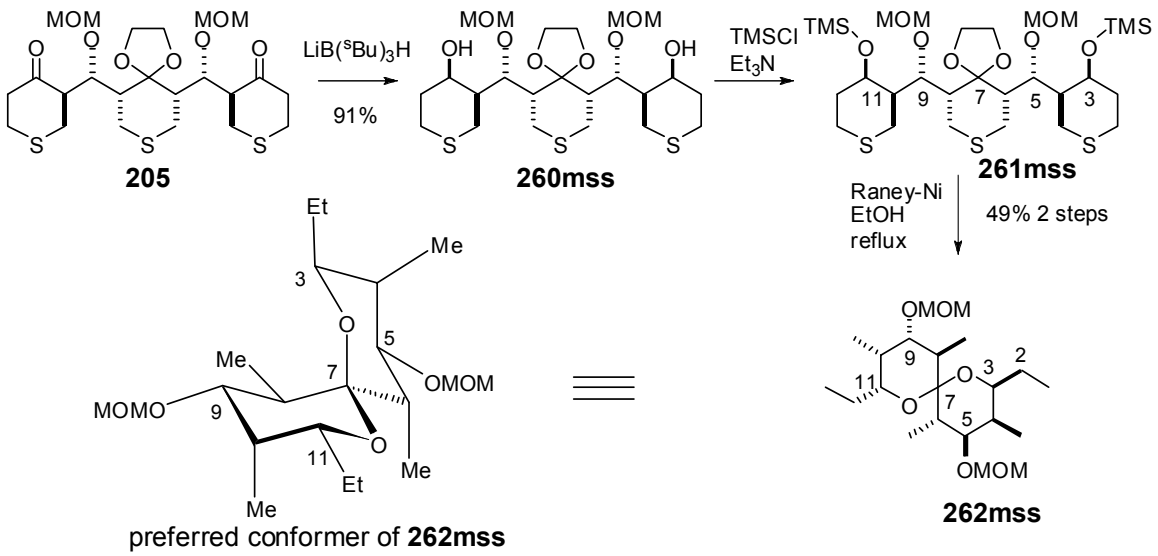
Figure 44: Proposed thiopyran based retrosynthetic analysis for enteridic acid

Desulfurization of **257** followed by hydrolysis of the ketal should afford **256** that should readily cyclize to furnish **254**. Alternatively, isomerization of **256** prior to cyclization will allow access to additional stereoisomers of **254**.

The main advantage of this strategy is the ease with which a large number of structurally complex stereoisomers can be rapidly constructed in only four carbon forming steps from the same precursor. This would allow for the creation of a library of stereoisomers for NMR comparison with the data reported for the natural product[9] in order to confirm or reassign the structure of enteridic acid. The stereoisomers could equally be used in SAR studies.

2.7.3.1 Synthesis of spiroketal adducts 262mss, 262as and 262maa.

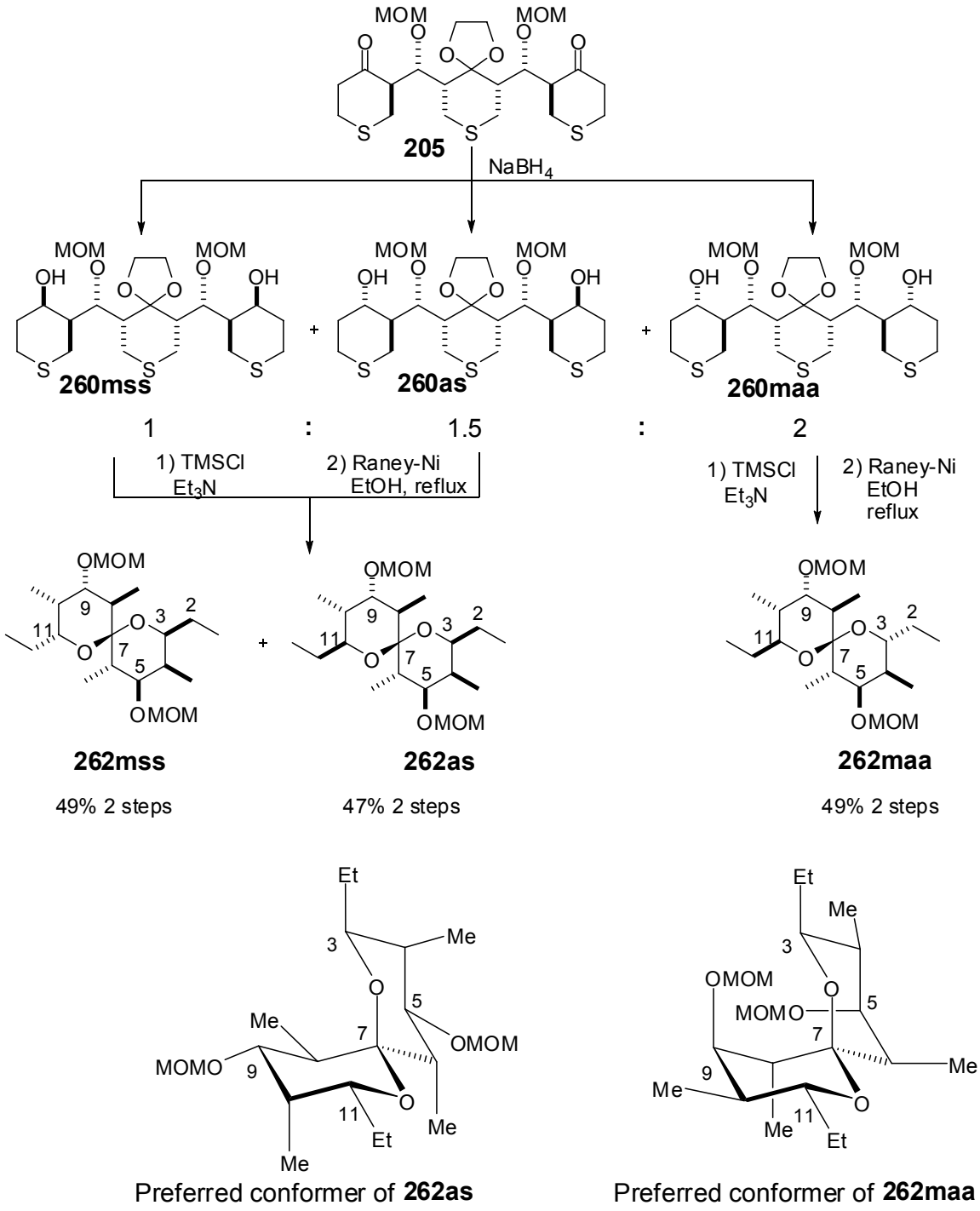
A series of three diastereomeric spiroketals having the C2-C11 carbon skeleton of enteridic acid were prepared according to the protocol described below. Stereoselective reduction of the *meso* diketone **205** using L-Selectride® furnished a single *meso* diol adduct **260mss** in 91% yield (Scheme 53). Protection of the diol **260mss** as the silyl enol ether followed by desulfurization afforded the spiroketal **262mss** in 49% yield over the two steps.



Scheme 53: Synthesis of the spiroketal **262mss**[‡‡‡].

A non-stereoselective reduction of the *meso* diketone **205** with $NaBH_4$ gave all three possible diastereomeric diol adducts in a 1:2:1.5 ratio. Only **260maa** could be obtained in pure form. Subjecting **260maa** to the previously estabilshed protection/desulfurization protocol gave **262maa** in 49% yield. Similar treatment of 1.5:1mixture of **260as** and **260mss**, respectively gave a separable mixture of **262as** and **262mss** (Scheme 54).

[‡‡‡] The numbering in the compounds in Scheme 53 is according to the numbering in enteridic acid.



Scheme 54: Synthesis of the spiroketals **262as** and **262maa**.

2.7.3.2 Structure determination of the of spiroketal adducts **262mss**, **262as** and **262maa**.

Unsymmetrical 1,7-Dioxaspiro[5.5]undecanes[§§§] can exist in four different chair–chair conformations (Figure 45). The relative stability of these conformers is influenced by three main factors: i) steric interactions between the substituents on the tetrahydropyran ring; ii) anomeric and related effects; iii) hydrogen bonding and other chelating effects.[179]

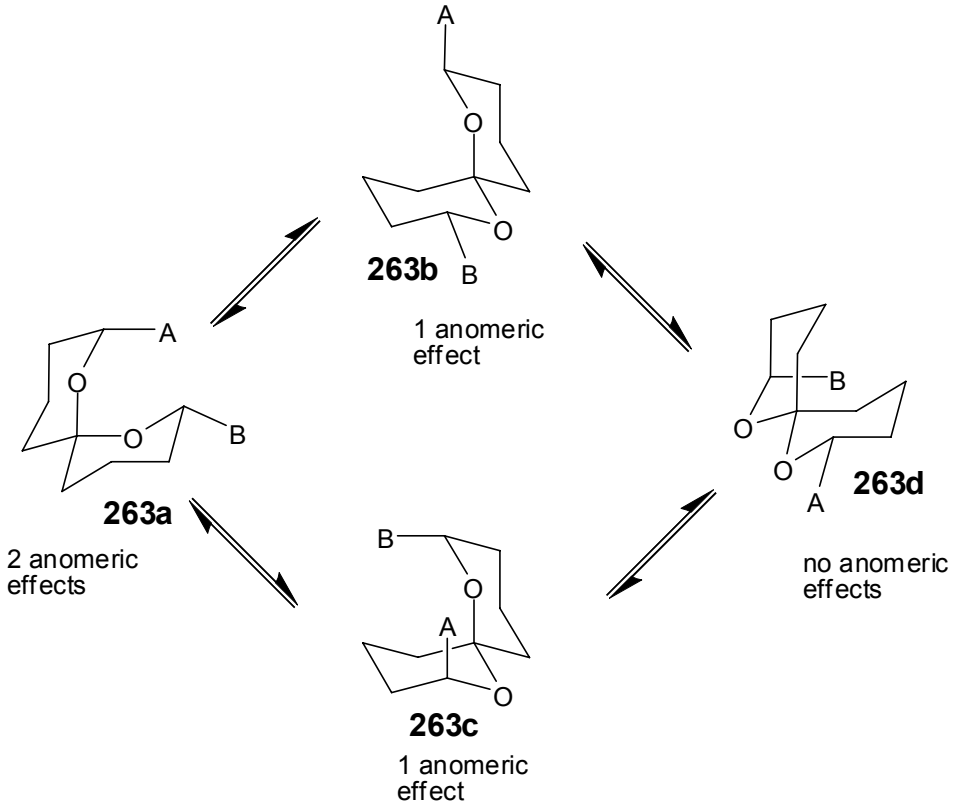


Figure 45: All the four possible chair-chair conformations of 1,7-Dioxaspiro[5.5]undecane

Compounds with alkyl groups on six membered rings typically favor chair conformations that place substituents in an equatorial orientation to avoid 1,3-diaxial interactions. In tetrahydropyran ring systems, this preference is balanced

[§§§] Formal name for six membered spiroketals.

in relation to the stabilizing consequences of anomeric effects. In compounds where both effects (i.e. steric and anomeric) are reinforcing, the preferred conformation can be easily predicted. However, in cases where these effects conflict the major conformer becomes more complicated to predict. Examples of both types abound in nature and the structures of these natural products were typically determined by NMR spectroscopic methods (usually involving ^{1}H-^{1}H coupling constants and NOE) and/or X-ray analysis for those compounds that are crystalline (Figure 46).[179,180]

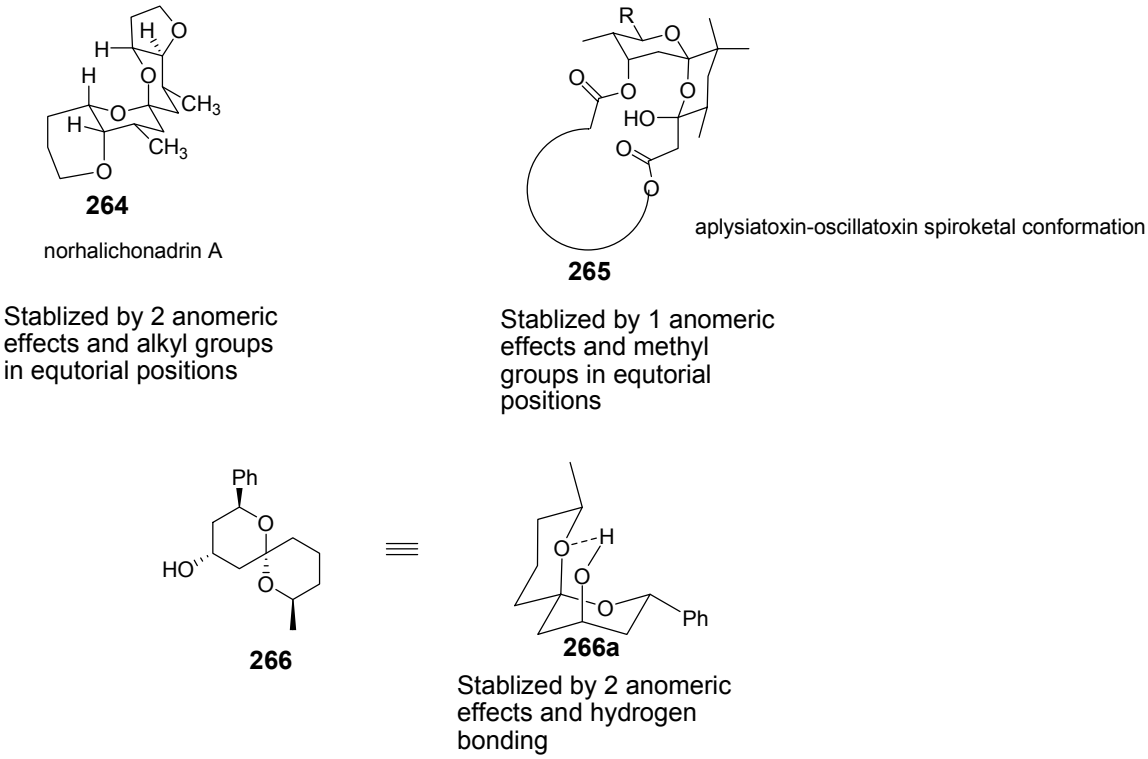


Figure 46: Examples of natural products with different stabilizing effects.

The structure of the spiroketals **262mss**, **262as** and **262maa** were determined by analysis of the ^{1}H-^{1}H coupling constants and NOE correlations and this analysis is discussed in the following subsections.

2.7.3.2.1 Determination of the conformation of the spiroketal adduct 262mss.

The spiroketal adduct **262mss** was the only adduct isolated from the desulfurization and cyclization process shown in Scheme 51. Only one spiroketal adduct (racemic) can be obtained from the meso starting material (assuming no isomerization). Adduct **262mss** can exist in four different conformations as shown in Figure 47.

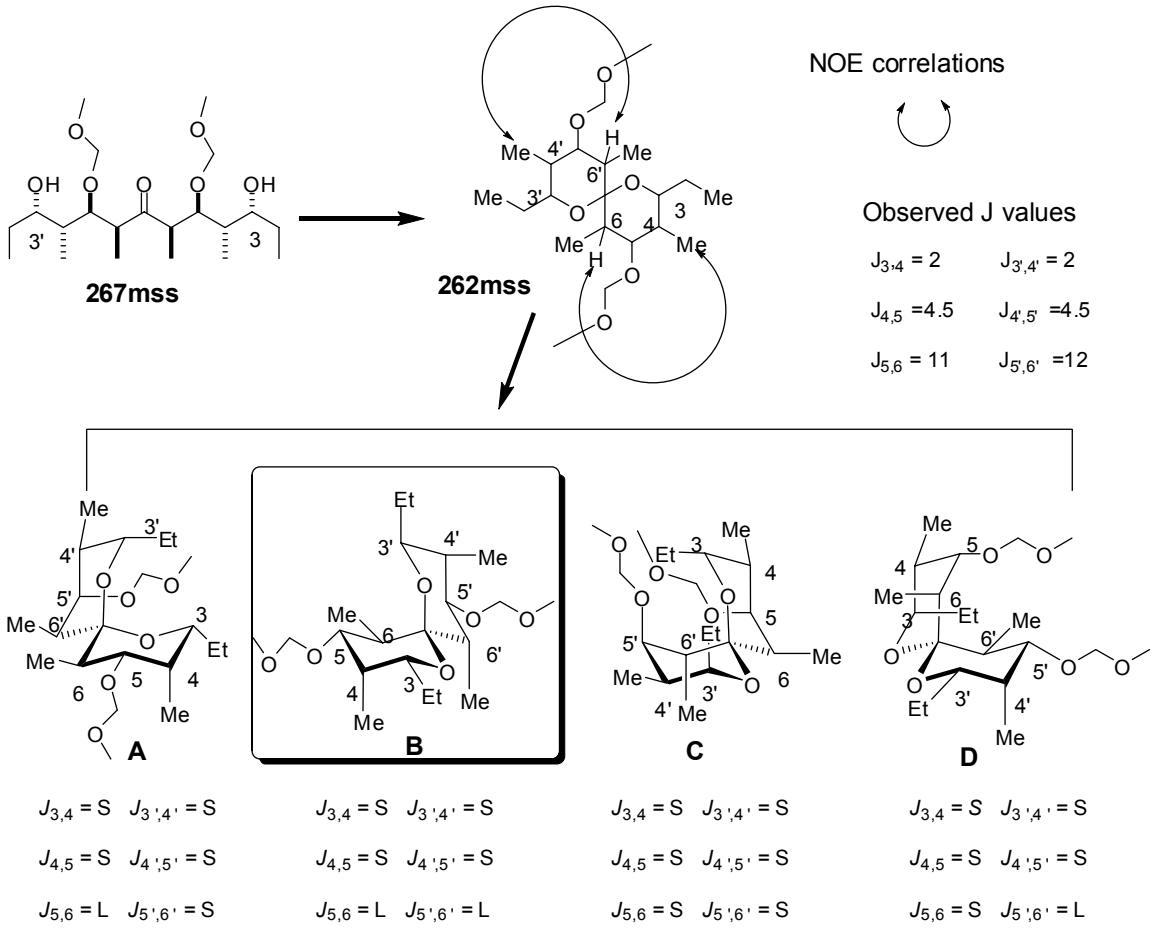


Figure 47: All possible conformations of **262mss**.

Comparison of the observed ^{1}H-^{1}H coupling constants with those expected from each of the conformers suggests that the conformer B best fits the data. A conformational search using Spartan predicted a 95% population for

conformer B in Figure 48. The NOESY experiment indicated correlations between HC-6 and CH_3C-4 and between HC-6' and CH_3C-4'. These correlations are possible only on conformer B. The combination of the three different data (i.e. coupling constants, conformational search and NOESY experiments) strongly indicates that the product **262mss** from the reaction described in Scheme 53 exists as conformer B in Figure 47.

2.7.3.2.2 Determination of the conformation of the spiroketal adduct 262maa.

The spiroketal adduct **262maa** was the only adduct isolated from the desulfurization and cyclization process shown in Scheme 54. Because the starting material **261maa** is *meso*, only one spiroketal adduct (racemic) can be obtained from this reaction in the absence of isomerization during the course of the reaction. Spiroketal adduct **262maa** can also exist in four different conformations as shown in Figure 48.

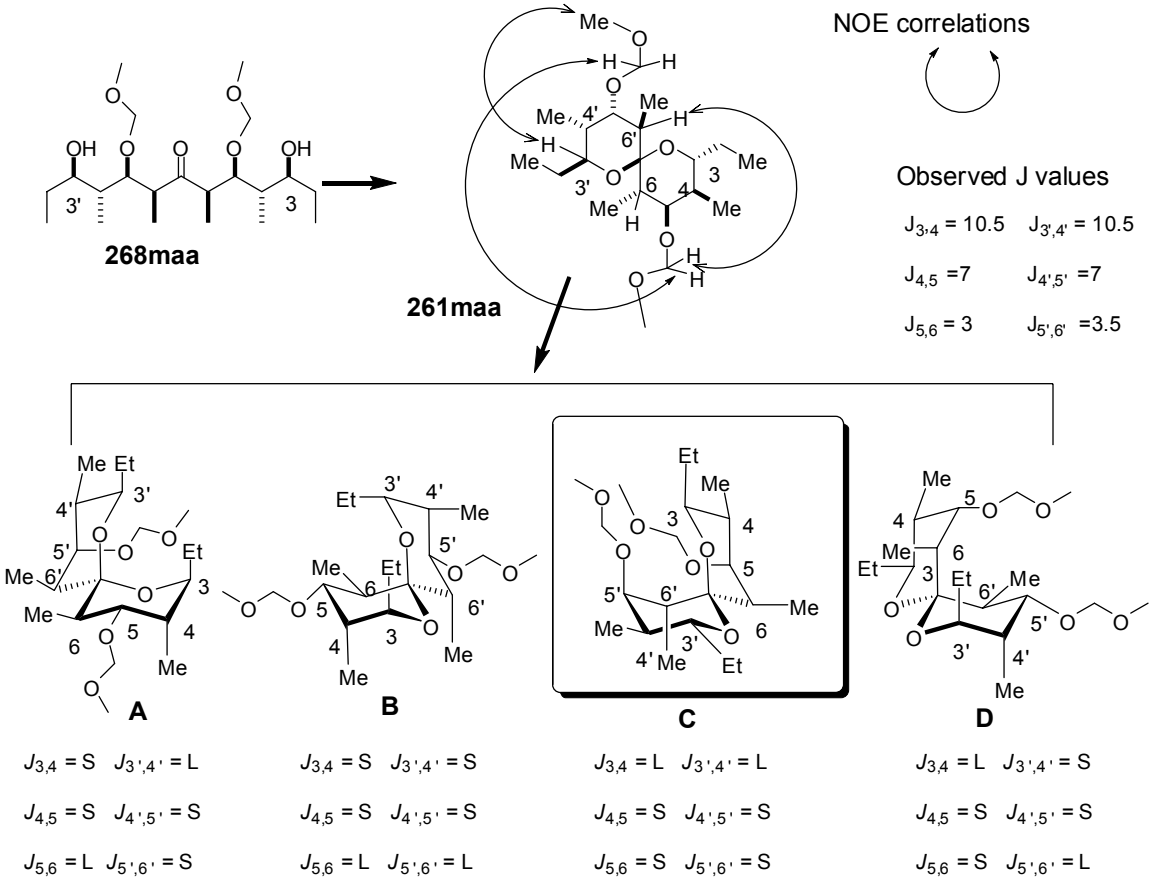


Figure 48: All possible conformations of **262maa**

Comparison of the observed ^1H-^1H coupling constants with those expected from each of the conformers suggests that the conformer C best fits the data. A conformational search using Spartan predicted a 95% population for conformer C (Figure 48). The NOESY spectrum indicated correlations between H6 on one ring and the OCH_2O protons on the other ring system, between H3 and OCH_3 on the same ring and more importantly a strong correlation between the OCH_2O groups. All these correlations are possible only in conformer C.

The combination of the three different data (i.e. coupling constant, conformational search and NOESY experiments) strongly indicates that the product isolated from the reaction described in Scheme 54 exists as conformer C in Figure 48.

2.7.3.2.3 Determination of the conformation of the spiroketal adduct 262as.

There are two possible racemic spiroketal adducts, **269as [1]** and **269as [2]** that can be formed from chiral racemic **260as** in the desulfurization and cyclization process shown in Scheme 55. These adducts differ in the relative configuration of the spirocenter. Each adduct can occur in four different conformations shown in series as 1 and 2 in Figure 49.

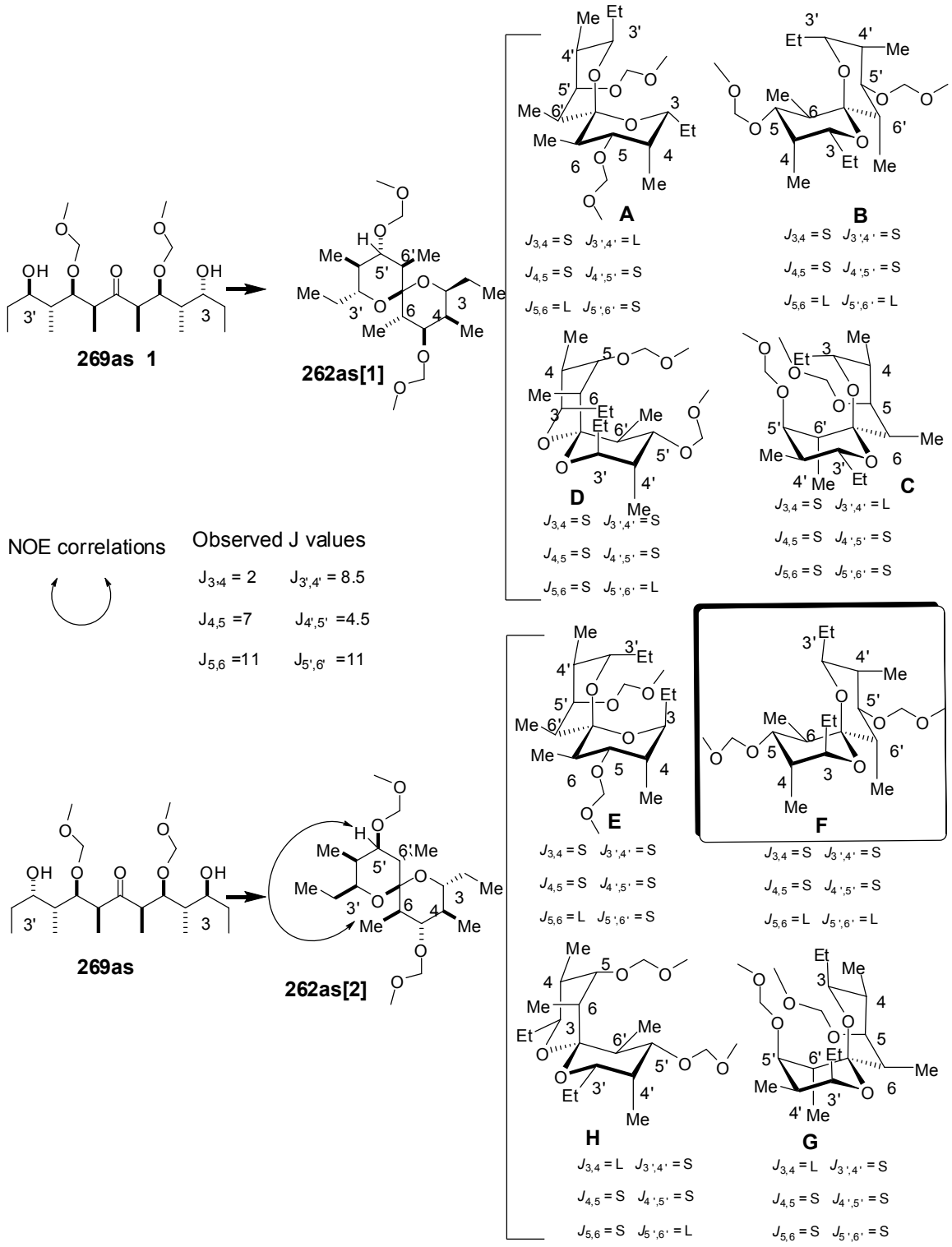


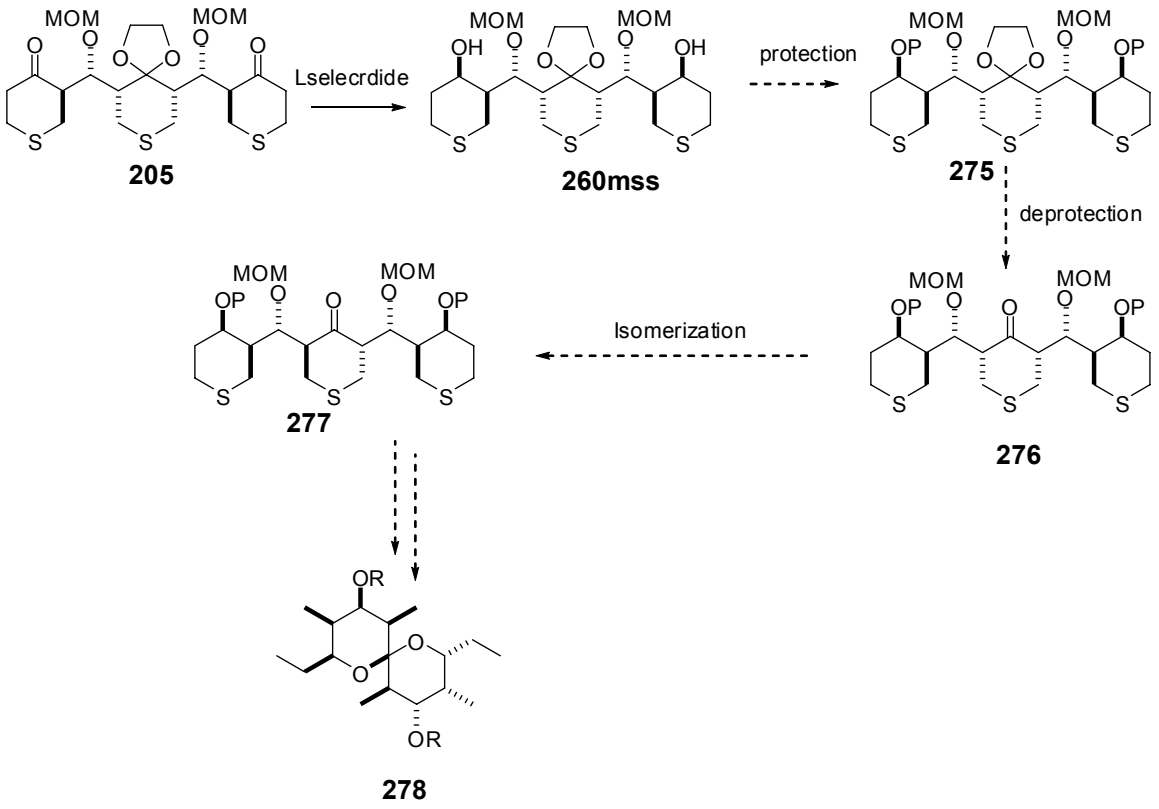
Figure 49: All possible conformations of **262as [1] and 262as [2].**

Comparison of the observed ^{1}H-^{1}H coupling constants with those expected for each of the conformers suggests that only conformer B and F can fit the data. Attempts to build the conformer B using Spartan show a high steric interaction between the C-3' ethyl group and C-6 methyl. The NOESY spectrum shows a strong correlation between H5' and C-6 methyl group. Interestingly a conformational search on **262as[1]** predicted that conformer A is the most stable (>95%). A similar analysis on **262as[2]** showed that conformer F was the most stable (>95%). Moreover, this analysis suggests that conformer A is 4 kcal mol^{-1} lower in energy than conformer F. Because the NMR data is consistent with conformer F but not with A, I must conclude that the spiroacetal formation of **269as** to **262as[2]** occurs under kinetic control.

2.7.6 Summary and Conclusions.

In summary, three spiroketal stereoisomers were successful prepared from the *meso* bis aldol adduct **205** towards the creation of a library of compounds as a means of confirming or reassigning the structure of enteridic acid. The protocol developed utilizes the Lewis acidic nature of metals (Ni-Al alloy, Raney nickel) as the catalyst for the cyclization process and, in all cases, gave a single diastereoisomer from the reaction. Conformational analysis of the spiroketal adducts (**262mss, 262as** and **262maa**) by molecular mechanics (using Spartan '04) suggested predominant conformers (>95%) that were consistent with the observed NMR data. In each case, a chair-chair conformation with one anomeric interaction is suggested. These results validate the method used to propose **253** as the correct structure for enteridic acid.

Due to time constrains, I was unable to complete the synthesis of **278**, the core spiroacetal structure of **253**. A proposed route to **278** is shown in Scheme 55. If the NMR data for **278** were a close match to the reported data for enteridic acid, then an enantioselective route to **253** based on Figure 42 could be attempted.



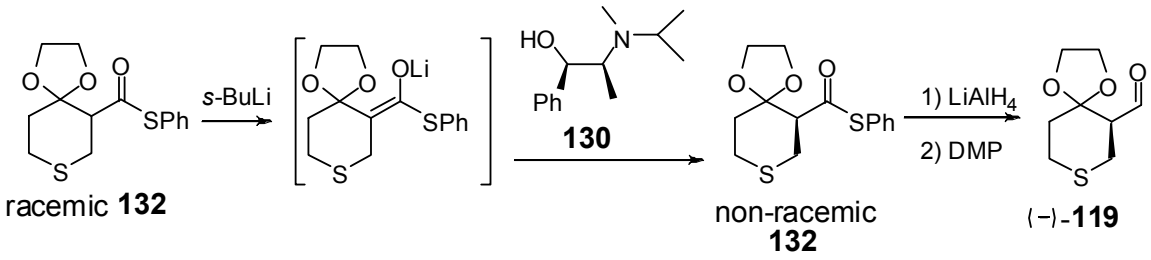
Scheme 55: Proposed route to the alternative core structure for enteridic acid structure.

Chapter 3

General summary and conclusions

Most of the research objectives listed in the introduction (Section 2.1.1) were achieved.

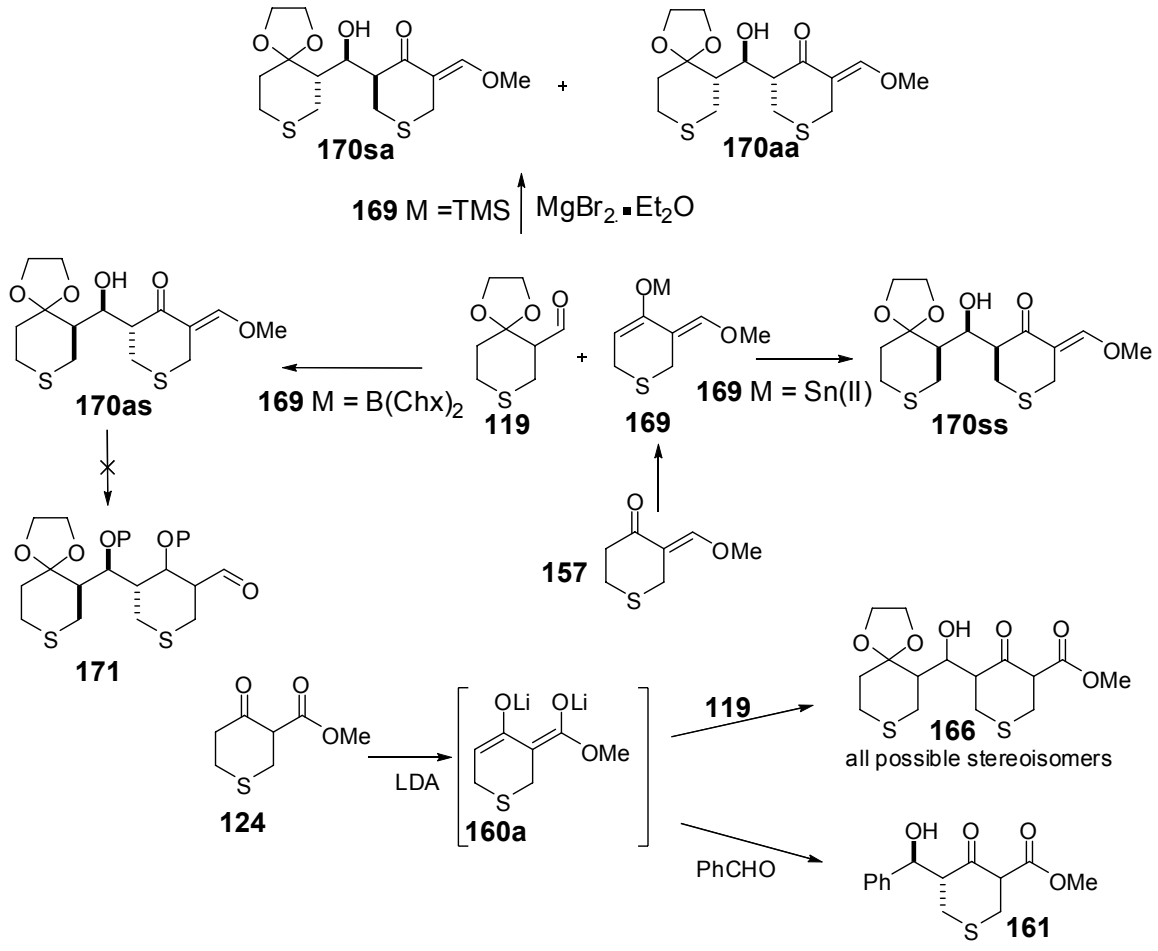
A protocol was successfully developed for the synthesis of the enantiopure aldehyde **119**. This protocol involves enantioselective protonation of the lithium enolate of **132** (generated from the reaction of *s*-BuLi) with the ephedrine derivate **130** followed by recrystallization, reduction, and oxidation (Scheme 56). In conclusion, a viable method was developed for the synthesis of the enantiomerically pure aldehyde **119**.



Scheme 56: Synthesis of enantiomerically pure **119.**

Two β-ketocarbonyl derivatives of thiopyranone capable of undergoing vinylogous aldol reactions were successfully prepared and their aldol reactions with aldehyde (±)-**119** were investigated. The selectivities observed from the aldol reactions of ketone **157** with **119** were similar to those previously obtained from the reactions of **112** with **119** under the same reaction conditions.[22]

All four possible aldol adducts **170** from the reaction of the **157** with **119** were successfully prepared (assuming the exocyclic olefin geometry is fixed and does not interchange in the course of the reaction) (Scheme 57). The aldol adduct **170as** was obtained selectively from the reaction of the boron enolate **121** with **119** and **170ss** was obtained selectively from the reaction of **119** with the Ti(IV) or Sn(II) enolate of **157** or from the $SnCl_4$ promoted reaction of **158** with **119**. These two adducts (**170**as and **170**ss) results from a 'Felkin' addition to the aldehyde **119.** The diastereoisomers **170sa** and **170aa** result from an 'anti Felkin' addition to the aldehyde **119** and were obtained from the $MgBr_2 \cdot Et_2O$ mediated reaction of **158** with **119**. Although the stereoselectivity of this reaction was low (1.5:1, in favour of **170sa**), a combination of isomerization (see Section 2.6) and fractionation could give either adduct in good overall yield.



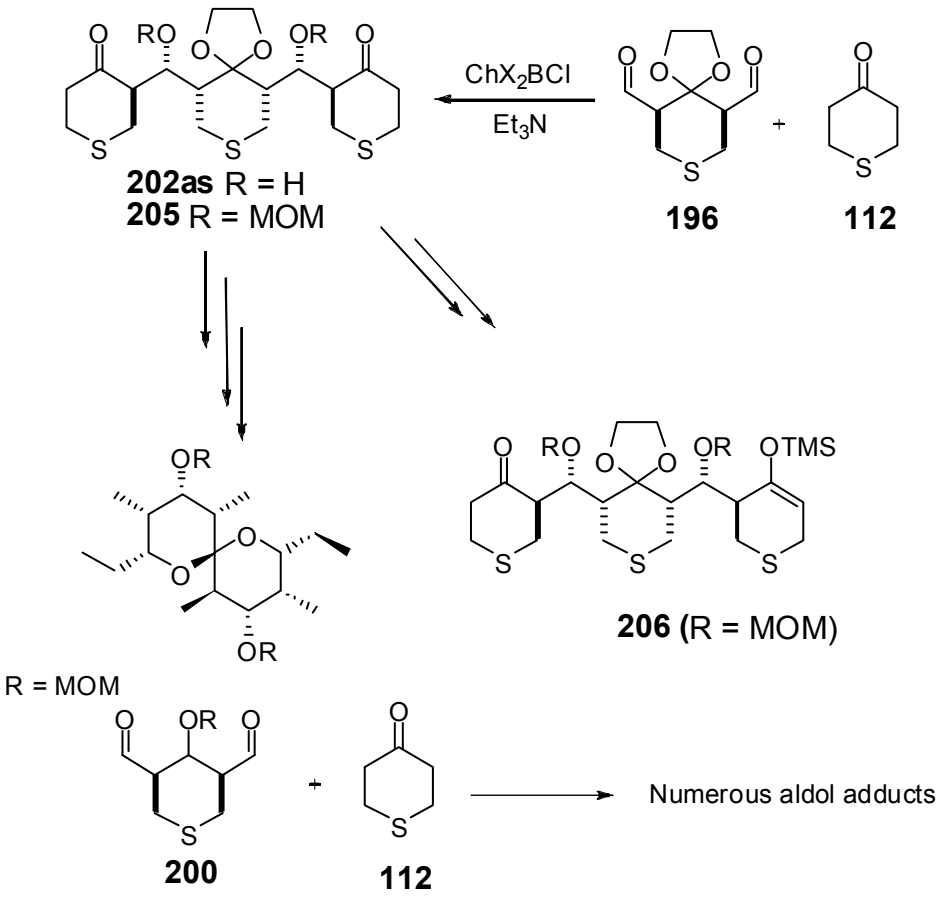
Scheme 57: Summary of approach 2 in the thiopyran route to polypropionate.

Attempts to transform aldol adduct **170** (or derivatives) into aldehydes (e.g. **171**) suitable for a second aldol coupling were unsuccessful. Likewise, despite considerable experimentation, the aldol adducts **170** (or derivatives) could not be transformed into tetrapropionate units suitable for natural product synthesis.

In conclusion the second approach shown in Figure 11 was investigated but was found not to be a suitable method for synthesizing hexapropionate units as at this time due to problems encountered in the second iteration step.

Likewise two stable *meso* dialdehydes **196** and **200** were synthesized and one (**196**) was successfully utilized to develop a protocol for a one pot two-directional aldol reaction generating **202as**, a *meso* adduct with six stereogenic centers. Attempts at using *meso* dialdehyde **200** under the same reaction conditions developed for **196** were not successful as numerous unidentifiable compounds were obtained from the reaction. Employing the methodology developed in the group,[163] the *meso* diketone **205** derived from **202as** was successfully desymmetrized via an enantioselective enolization reaction to afford the chiral mono enol ether **206** in 71% isolated yield (>95% based on recovered **205**) with 95% ee (Scheme 58). The *meso* diketone **205** was employed in generating a series of spiroketal adducts that was used to validate the result of computational studies used to propose a new structure for enteridic acid.

In conclusion, this approach was successfully shown to be a viable method for the synthesis of enantiomerically pure hexapropionate units.

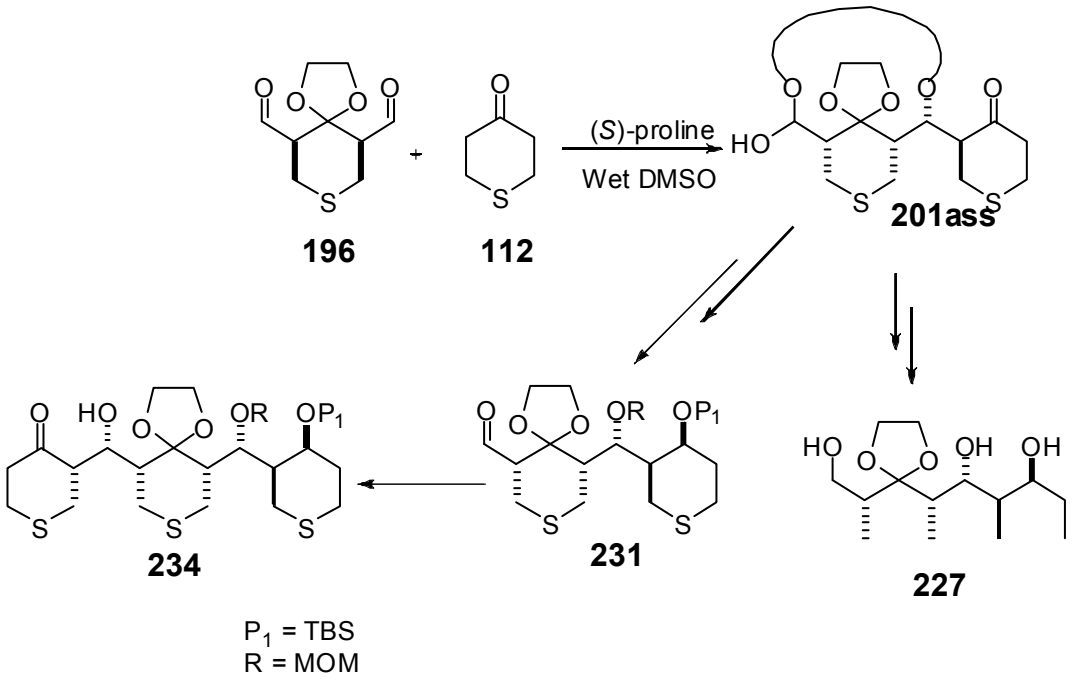


Scheme 58: Summary of the 3rd approach in the thiopyran route to polypropionate.

The *meso* dialdehyde **196** was also successfully desymmetrized via aldol reaction catalyzed by proline. The unusually high stereoselectivity observed in the reaction result from the combination of both the high facial bias imposed by the reagent and the high intrinsic Felkin diastereoselectivity in the β-ketal aldehyde. This reaction combines a dynamic kinetic resolution and a thermodynamic process to afford a single product in good yield and good ee (Scheme 59).

The aldol adduct was successfully converted to a tetrapropionate fragment that could be applied in the syntheses of natural products. Conversion of the aldol adduct **201ass** to an aldehyde suitable for a second aldol coupling was also achieved. A second aldol coupling was carried out to give a mixture of

2 out of the 4 possible aldol adducts in high yield. These two enantioenriched hexapropionate building blocks can also be used in natural product synthesis.



Scheme 59: Summary of the use of *meso* **196** in an enantiotopic group selective aldol reaction.

Chapter 4

Experimental

4.1 General methods

All solvents were distilled prior to use. Anhydrous solvents were distilled under argon atmosphere as follows: tetrahydrofuran (THF) from benzophenone sodium ketyl; ether from benzophenone sodium ketyl; CH_2Cl_2, $CHCl_3$ and toluene from CaH_2; MeOH from $Mg(OMe)_2$; benzene from sodium metal and stored over 5Å molecular sieves and dimethyl sulfoxide was stored over 5Å molecular sieves for 1 week prior to use. All experiments involving air- and/or moisture-sensitive compounds were conducted in an oven dried round-bottom flask capped with a rubber septum, and attached via a needle and connecting tubing to an argon manifold equipped with mercury bubbler (ca. 5 mm positive pressure of argon). Low temperature baths were ice/water (0 °C) CO_2(s)/acetone (-78 °C) and liquid nitrogen/ether (-100 °C). Reaction temperatures refer to that of the bath.

Preparative TLC (PTLC) was carried out on glass plates (20 × 20 cm) precoated (0.25 mm) with silica gel 60 F254. Materials were detected by visualization under an ultraviolet lamp (254 nm) and/or by treating a 1 cm vertical strip removed from the plate with a solution of phosphomolybdic acid (5%) containing a trace of cerium sulfate in aqueous sulfuric acid (5% v/v), followed by charring on a hot plate. Concentration refers to removal of volatiles at water aspirator pressure on a rotary evaporator. Unless otherwise noted, all reported compounds were homogeneous by thin layer chromatography (TLC)

and by NMR. Flash column chromatography (FCC) was performed according to Still *et. a.l.*[181] with Merck Silica Gel 60 (40-63 μm). Medium pressure chromatography (MPC) was performed as reported by Taber.[182] Dry flash column chromatography (DFC) was performed according to Harwood.[183] All mixed solvent eluents are reported as v/v solutions. Quantitative internal standard refers to a known volume of a solution of 1,2-dimethoxybenzene in C_6D_6 (2.0 g in 10 mL).

High resolution mass spectra (HRMS) and low resolution mass spectra (LRMS) were obtained on a VG 70E double focusing high resolution spectrometer; only partial data are reported. EI ionization was accomplished at 70 eV and CI at 50 eV with ammonia as the reagent gas; only partial data are reported. IR spectra were recorded on a Fourier transform interferometer using a diffuse reflectance cell (DRIFT); only diagnostic and/or intense peaks are reported. Unless otherwise noted, NMR spectra were measured in CDCl3 solution at 300, 400, or 500 MHz for ^{1}H and 75, 100, or 125 MHz for ^{13}C. Signals due to the solvent (^{13}C NMR) or residual protonated solvent (^{1}H NMR) served as the internal standard: $CDCl_3$ (7.27 δH, 77.23 δC); CD_3OD (3.31 δH, 49.15 δC); C_6D_6 (7.16 δH, 128.39 δC). The ^{1}H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), brs (broad singlet), ap (apparent); the list of couplings constants (*J*) corresponds to the order of the multiplicity**** assignment. Couplings constants (*J*) are reported to the nearest 0.5 Hz. The ^{1}H NMR assignments were made based on chemical shift and multiplicity and were confirmed, where necessary, by homonuclear decoupling and/or NOE experiments. The ^{13}C NMR assignments were made on the basis of chemical shift and multiplicity (as determined by *J*-modulation[184] or HSQC[185]) and were confirmed, where necessary, by two dimensional ^{1}H/^{13}C correlation experiments (HSQC and/or HMBC[186]).

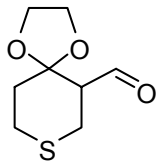
**** The multiplicity of ^{13}C NMR signals refers to the number of attached H's (i.e., s = C, d = CH, t= CH_2, q = CH_3)

All other reagents were commercially available and unless otherwise noted, were used as received.

4.2 Experimental procedure and spectral data of synthesized compounds

Compounds **124**, **125** and **126** were prepared according to established procedures within the group and their spectra data were consistent with that reported.[22]

1,4-Dioxa-8-thiaspiro[4.5]decane-6-carboxaldehyde (119).[22]

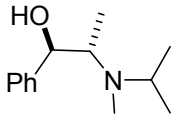


119

The published procedure was modified as follows for the preparation of **119**;

Neat DMSO (13.6 mL, 182 mmol) was added dropwise via syringe to a stirred solution of oxalyl chloride (7.9 mL, 91 mmol) in CH_2Cl_2 (300 mL) at -78 °C under argon. After 30 min at -78 °C, a solution of **118** (15.8 g, 82.9 mmol) and DMS (12.2 mL, 166 mmol) in CH_2Cl_2 (20 mL) was added rapidly via syringe to the reaction mixture. After another 30 min, *i*-Pr_2EtN (43.7 mL, 249 mmol) was added, and the reaction mixture was allowed to warm to -10 over 30 min. The mixture was poured into aqueous 10% HCl (250 mL), the organic layer separated and the aqueous extracted with CH_2Cl_2 (100 mL x 2). The combined organic layers were washed with and $NaHCO_3$, dried over Na_2SO_4, and concentrated. Fractionation by DFC (35% ethyl acetate in hexane) gave **119** as a pale-yellow oil (13.0 g, 83%). The spectra data were consistent with that reported.[22]

(1*R*, 2*S*)-2-(*N*-isopropyl-*N*-methylamino)-1-phenylpropan-1-ol [187]



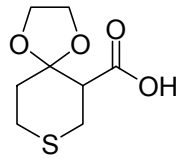
(+)**-130**

Compound **130** was prepared according to published procedure [187]

A mixture of **139** (5.53 g, 28.6 mmol), aq HCHO (37 % in water) (43 mL), and formic acid (30 mL) was heated under reflux for 7 h to give a white cloudy solution. 2 N NaOH aq (320 mL) and MeOH (138 mL) was added and refluxing continued for another 1 h within which the reaction mixture turned into a brick-red clear solution. The reaction mixture was extracted with ether (100 mL x 4); the combined organic phase dried (Na_2SO_4), concentrated and distilled using a bulb-bulb apparatus (150 ^oC, 0.25 torr) to afford the titled compound (4.5 g, 77%, $[\alpha]^{24}_D$ +2.5 (*c* = 6, $CHCl_3$).

Lit[129,131] $[\alpha]^{24}_D$ +2.1 (*c* = 6, $CHCl_3$).

1,4-Dioxa-8-thia-spiro[4.5]decane-6-carboxylic acid (131).[120]

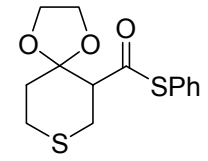


131

Aqueous NaOH (0.75 M; 150 mL, 0.11 mol) was added to a stirred solution of **125** (16.01 g, 0.073 mol) in MeOH (40 mL) at ambient temperature (exothermic). After 1.5 h, the mixture was cooled to 0 ^oC, acidified to pH 1 by addition of conc.

HCl and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give (±)-**131** as a white solid (14.55 g, 97%) that was homogeneous by ^{1}H NMR. Recrystallization (CH_2Cl_2/hexane; 1:15) yielded (±)-**131** as white needles (13.35 g, 89%; mp 101–102 ^oC). The spectral data were consistent with that previously reported.

S-Phenyl 1,4-Dioxa-8-thia-spiro[4.5]decane-6-carbothioate (132)[120]



(±)-**132**

Oxalyl chloride (5.4 mL, 62 mmol) was added dropwise to a stirred solution of (±)-**131** (8.42 g, 41.2 mmol) in benzene (80 mL) at room temperature under argon. After 3h, the mixture was concentrated and thiophenol (4.50 mL, 43.7 mmol) and Et_3N (11.5 mL, 83.7 mmol) added sequentially to a stirred solution of the residue in THF (130 mL) (a white precipitate formed). After 15 min, the mixture was filtered through a mixture of basic Al_2O_3 and Celite and the combined filtrate and washings concentrated to give (±)-**132** as a white solid (11.8 g, 96%) that was homogeneous by ^{1}H NMR. Recrystallization from ether gave analytically pure (±)-**132** (10.5 g, 86%; mp 80–82 ^oC).

IR (DRIFT) ν_{max}: 1690 cm^{-1}

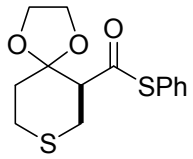
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.40 (5H, s, Ph), 4.03–3.93 (4H, m, H_2CO x 2), 3.28–3.22 (2H, m, HC-6, HC-7), 2.93–2.86 (2H, m, HC-7,HC-9), 2.63 (1H, dddd, *J* = 2, 3.5, 5.5, 13.5 Hz, HC-9),2.15 (1H, ddd, *J* = 3, 5.5, 13.5 Hz, HC-10), 1.87 (1H,ddd, *J* = 3.5, 11.5, 13.5 Hz, HC-10).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 195.6 (s), 134.5 (d·2), 129.5 (d), 129.3 (d·2), 127.9 (s), 107.7 (s), 65.4 (t), 65.2 (t), 59.7(d), 37.4 (t), 30.1 (t), 26.8 (t).

LRMS (EI), *m/z* (relative intensity): 296 ([M^+] 13), 187 (68), 159 (20), 109 (12), 99(100), 55 (25).

HRMS *m/z* calcd for $C_{14}H_{16}O_3S_2$ 296.0541, found 296.0543.

Anal. Calcd for $C_{14}H_{16}O_3S_2$: C, 56.73; H, 5.44. Found: C, 56.79; H, 5.59.

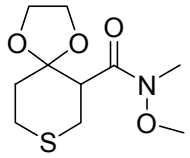


(-)-**132**

Enantioselective protonation: s-BuLi (1.1 M in hexanes; 6.2 mL, 6.8 mmol) was added dropwise via syringe over 5 min to a stirred solution of (±)-**132** (1.02 g, 3.44 mmol) in THF (165 mL) at -78 ^oC under argon. After 15min, the mixture was cooled to -100 ^oC and after 15 min, a solution of (1S,2R)-(+)-N-isopropylephedrine (+)-**130** (3.4 g, 18.9 mmol) in THF (5 mL) was added at once via syringe. The mixture was allowed to warm slowly to -78 ^oC over 40 min and after 2h at that temperature, the reaction quenched by addition of water (5 mL). The cooling bath was removed and after 15min, the mixture was diluted with aqueous HCl (2 M) and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (50% EtOAc in hexane) to give (-)-**132** as a white solid {1.01 g, 99%; $[\alpha]^{24}_D$ -14, (*c* 1.0, $CHCl_3$); 82% ee}. Recrystallization (x 2) of this sample from ether gave (-)-**132** {0.516 mg, 51%; mp 76–78 ^oC; $[\alpha]^{24}_D$ -18, (*c* 1.0, $CHCl_3$); 95% ee}. A sample of (-)-**132** with >98% ee was obtained by further crystallization {mp 78–79 ^oC; $[\alpha]^{24}_D$ -19, (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{14}H_{16}O_3S_2$: C, 56.73; H, 5.44. Found: C, 56.73; H, 5.64}.

The mother liquors from above were combined and concentrated to give (-)-**132** (0.490 g, 48%; *ca*. 65% ee). To recover (+)-**130**, the aqueous phase was made basic (pH *ca*. 12) by addition of 30% aqueous NaOH and then extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated, and the reddish-brown residue subjected to bulb-to-bulb distillation (150 ^oC, 0.4 mbar) to afford (+)-**130** as a pale yellow oil {3.2 g, 94%;$[\alpha]^{24}_D$ +2.5, (*c* 6.0, $CHCl_3$)}. Reduction of **132** gave **126** whose ee was determined by ^1H NMR of the derived Mosher's ester. (-)-**132** is assigned the (*R*)-configuration because $LiAlH_4$ reduction of (-)-**132** gave (*R*)-(+)-**126** of established absolute configuration.[120]

***N*-Methoxy-*N*-Methyl-1,4-dioxa-8-thia-spiro[4.5]decane-6-carboamide (133).**



133

Compound **133** was prepared according to a modified published procedure;[188]

Oxalyl chloride (0.273 mL, 3.15 mmol) was added dropwise to a stirred solution of **131** (430 mg, 2.11 mmol) in benzene (2.4 mL) at room temperature under argon. After 3h, the mixture was concentrated and a freshly prepared solution of HNMe(OMe) (5 mL) in CH_2Cl_2 {prepared from HNMe(OMe).HCl (364 mg, 2.32 mmol) and DIEA (605 mL, 3.47 mmol) in CH_2Cl_2 at 0 ^oC for 1 h} and DIEA (550 mL, 3.16 mmol) was added sequentially to a stirred solution of the residue in CH_2Cl_2 (5 mL). After 30 min, the mixture was diluted with CH_2Cl_2 (20 mL), washed with water (10 mL), dried (Na_2SO_4) and concentrated to give the titled compound as a white solid that is homogenous by ^1H NMR (474 mg, 91%).

IR (DRIFT) ν_{max}: 2969, 1663, 1419, 1383, 1258, 1150, 1103, 1049 cm^{-1}.

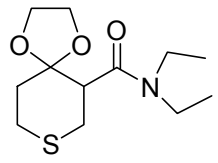
^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.04-3.88 (4H, m, HC-2'', 2'', 3'', 3''), 3.74 (3H, br s, H_3CO), 3.46 (1H, m), 3.26 (1H, m), 3.20 (3H, br s, H_3C), 2.98 (1H, ddd, *J* = 3, 11.5, 13.5 Hz), 2.66 (1H, m), 2.61 (1H, m), 2.19 (1H, m), 1.85 (1H, ddd, *J* = 3.5, 11.5, 13.5 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.1, 108.2, 65.3, 65.1, 61.5, 46.9, 37.8, 31.4, 29.8, 27.0

LRMS (EI), *m/z* (relative intensity): 247 ($[M]^+$, 18), 187 (20), 159 (11), 148 (11), 132 (10), 113 (5), 99 (100), 54 (24).

HRMS *m/z* calcd. for $C_{10}H_{17}NO_4S$: 247.0878; found: 247.0880.

***N,N*-Diethyl-1,4-dioxa-8-thia-spiro[4.5]decane-6-carboamide (134).**



134

Oxalyl chloride (0.323 mL, 3.73 mmol) was added dropwise to a stirred solution of **131** (507 mg, 3.73 mmol) in benzene (5 mL) at room temperature under argon. After 3 h, the mixture was concentrated and Et_2NH (1.02 mL, 7.45 mmol) added to a stirred solution of the residue in THF (10 mL) (a white precipitate formed). After 15 min, the mixture was filtered through a mixture of basic Al_2O_3 and Celite

and the combined filtrate and washings concentrated to give the titled compound as a homogenous oil that was homogeneous by ^{1}H NMR (541 mg, 84%).

IR (DRIFT) ν_{max}: 1630, 1337, 1427, 1235, 1151, 1092, 1050 cm^{-1}.

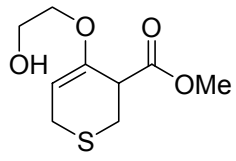
^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.06-3.70 (6H, m), 3.44 (1H, dd, *J* = 12, 12 Hz), 3.26-3.01 (4H, m), 2.63-2.56 (2H, m), 2.11 (1H, ddd, *J* = 3.5, 3.5, 13 Hz), 1.89 (1H, ddd, *J* = 3.5, 13, 13 Hz), 1.21 (3H, t, *J* = 7 Hz, CH3), 1.13 (3H, t, *J* = 7 Hz, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.3, 108.6, 65.4, 65.3, 49.0, 42.2, 40.3, 39.0, 30.3, 27.0, 14.7, 13.0.

LRMS (EI), *m/z* (relative intensity): 259 ([M]$^+$, 79), 214 (52), 159 (75), 132 (22), 126 (61), 115 (35), 99 (100), 72 (26).

HRMS *m/z* calcd. for $C_{12}H_{21}NO_3S$: 259.1242; found: 259.1242.

Methyl 3,6-dihydro-4-(2-hydroxyethoxy)-2H-thiopyran-3-carboxylate (136).[120]



136

LDA was prepared by addition of BuLi (2.5 M in hexanes; 8.4 mL, 21 mmol) to a stirred solution of i-Pr_2NH (2.33 g, 23 mmol) in THF (65 mL) at 0 ^{o}C under argon. The mixture was cooled to -78 ^{o}C and a solution of the ketal ester **125** (1.46 g,

6.72 mmol) in THF (2 mL) added dropwise via syringe. After 30 min, the reaction was quenched by addition of H_2O (10 mL) and the mixture diluted with brine and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (50% EtOAc in hexane) to yield the titled compound as light yellow oil (1.37 g, 94%).

IR (DRIFT) v_{max}: 3435, 1731, 1666 cm^{-1}

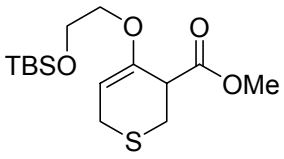
^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.42 (1H, dd, *J* = 3.5, 4.5 Hz, HC-5), 3.68–3.42 (4H, m, H_2CO x 2), 3.25 (3H, s, H_3CO), 3.16 (1H, dd, *J* = 4.5, 5 Hz, HC-3), 2.94 (1H, dd, *J* = 5, 13.5 Hz, HC-2), 2.90 (1H, br d, *J* = 16.5 Hz, HC-6), 2.75 (1H, dd, *J* = 4.5, 16.5 Hz, HC-6), 2.50 (1H, dd, *J* = 4.5, 13.5 Hz, HC-2).

^{13}C NMR (500 MHz, $CDCl_3$) δ: 172.2, 152.7, 96.4, 68.9, 60.9, 52.3, 45.9, 28.5, 25.1.

LRMS (EI), *m/z* (relative intensity): 218 ($[M]^+$ 13), 190 (10), 173 (100), 158 (19), 140 (46), 115 (37), 99 (31), 86 (9)

HRMS *m*/z calcd for $C_9H_{14}O_4S$ 218.0613, found 218.0611.

Methyl 3,6-dihydro-4-[2-(dimethyl(1,1-dimethylethyl)silyloxy)ethoxy]-2H-thiopyran-3-carboxylate (137).[120]



137

$^{t}BuMe_2SiCl$ (802 mg, 5.17 mmol), Et_3N (1.4 mL, 10 mmol), and DMAP (29 mg, 0.24 mmol) were sequentially added to a stirred solution of the hydroxyl ester **136** (1.02 g, 4.70 mmol) in CH_2Cl_2 (20 mL) under argon. After 18h, MeOH (5 mL) was added and the mixture washed with brine. The aqueous layer was extracted with CH_2Cl_2 and the combined CH_2Cl_2 layers dried over Na_2SO_4, concentrated, and the residue passed through a short silica pad eluting with 30% EtOAc in hexane to afford the titled compound as a light yellow oil (1.46 g, 94%).

IR (DRIFT) ν_{max}: 1743, 1671 cm^{-1}

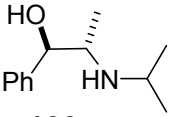
^{1}H NMR (500 MHz, C_6D_6) δ: 4.53 (1H, dd, *J* = 4, 4 Hz, HC-5), 3.73–3.63 (2H, m, H_2CO), 3.56–3.50 (2H, m, H_2CO), 3.39 (3H, s, H_3CO), 3.34 (1H, dd, *J* = 4.5, 5.5 Hz, HC- 3), 2.98 (1H, dd, *J* = 5.5, 13.5 Hz, HC-2), 2.92–2.84 (2H, m, HC-6), 2.58 (1H, dd, *J* = 4.5, 13.5 Hz, HC-2), 0.90 (9H, s, $C(CH_3)_3$), 0.07(6H, s, CH_3Si x 2).

^{13}C NMR (125 MHz, C_6D_6) δ: 171.6 (s, CO), 153.6 (s, C-4), 95.5 (d, C-5), 68.90 (t, C-30), 62.4 (t, C-20), 52.0 (q, CH_3O), 46.3 (d, C-3), 29.0 (t, C-2), 26.4 (q x 3, $(CH_3)_3C$), 25.2 (t, C-6), 18.9 (s, $C(CH_3)_3$), -4.8 (q, CH_3Si), -4.8 (q, CH_3Si).

LRMS (EI), *m/z* (relative intensity): 317 ($[M-CH_3]^+$, 3), 275 ($[M-C_4H_9]^+$, 19), 257 (19), 229 (22), 213 (11), 173 (33), 89 (33), 73 (100).

HRMS *m/z* calcd for $C_{15}H_{28}O_4SSi$ 332.1478 (275.0773 for $M-C_4H_9$), found 275.0767 ($M-C_4H_9$)

(1*S*,2*R*)-2-(Isopropylamino)-1-Phenylpropan-1-ol (139).[189]



139

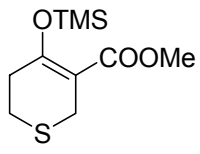
Compound **139** was prepared according to published procedure.[189]

A mixture of norephedrine (**138**) (4.43 g, 29.3 mmol) in EtOH (9.4 mL) and acetone (3.3 mL) was stirred at ambient temperature for 5 h. $NaBH_4$ powder (2.23 g, 59.0 mmol) was added in one portion to the reaction mixture and allowed to stir at the same temperature for another 1.5 h. The reaction mixture was quenched slowly with 6 M HCl to pH 1 (caution: evolution of gas!), concentrated, the residue re-dissolved in water (50 mL) followed by filtration to remove un-dissolved matter. The filtrate was basified to pH 14 using aq 10 M NaOH, extracted with ether (100 mL x 4), the combined organic phase was then dried over Na_2SO_4 and concentrated to give a white solid that is homogeneous by TLC and ^{1}H NMR (5.5 g, 97%). Recrystallization from petroleum ether (40-60 ^oC) gave 4.53 g, 80%, mpt 85-87 ^oC).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.36-7.24 (5H, m, Ar), 4.68 (1H, d, *J* = 4 Hz, HC-3), 3.05 (1H, dq, *J* = 4, 6.5 Hz, HC-2), 2.97 (1H, sep, HC (N)), 1.11 (3H, d, *J* = 6.5 Hz, H_3C), 1.09 (3H, d, *J* = 6.5 Hz, H_3C), 0.80 (3H, d, *J* = 6.5 Hz, HC-1).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 141.8, 128.2, 127.2, 126.4, 73.7, 55.3, 45.9, 23.9, 15.6.

Methyl 5,6-dihydro-4-(trimethylsiloxy)-2*H*-thiopyran-3-caboxylate.



143

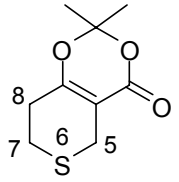
To a stirred solution of the ß-ketoester **124** (988 mg, 5.67 mmol) in benzene (20 mL) was added sequentially TMSCl (1.08 mL, 8.51 mmol) and Et_3N (1.19 mL,

8.51, mmol). The mixture was allowed to stir at room temperature for 24 h, filtered through celite, concentrated and distilled (100 °C at 0.5 torr) to afford the title compound (1.25 g, 90%).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.74 (3H, br s, OCH_3), 3.44 (2H, br s, HC-2), 2.75 (2H, t, *J* = 6 Hz, HC-6), 2.46 (2H, t, *J* = 6 Hz, HC-5), 0.24 (9H, br s, $(CH_3)_3$)

^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.9, 160.3, 109.1, 51.2, 33.8, 26.2, 25.5, 0.6.

7,8-Dihydro-2,2-dimethylthiopyrano[4,3-d][1,3]dioxin-4(5H)-one.



154

Prepared according to published procedure;[138]

To a stirred solution of ketoester (106 mg, 0.61 mmol) in MeOH (1 mL) was added 15% KOH (5 mL) at 0 °C. After 4 h, the mixture was poured into an ice bath and acidified to pH 1 using conc. HCl. The aqueous solution was extracted with ether (50 mL x 3), dried (Na_2SO_4) and concentrated without heat to afford **153** (85 mg, 87%) as a white solid that is homogeneous by TLC and was used without any further purification.

To a suspension of the keto acid **153** (85 mg, 0.53 mmol) in acetone (2 mL) at -78 °C was added Ac_2O (0.15 mL, 1.58 mmol) and 1 drop of conc H_2SO_4. The mixture was kept at 5 °C for 12 h. The now homogeneous mixture was poured into a beaker containg ice cold 10% Na_2CO_3 and the mixture stired for 30 min while warming up to room temperature. The mixture was extracted with ether (20 mL x 2), dried (Na_2SO_4), concentrated and fractionated by FCC (30% EtOAc in hexanes) to afford the titled compound as a white solid (29.5 mg, 30%).

IR (DRIFT) v_{max}: 3001, 2912, 1722, 1651, 1407, 1276, 1199, 1151 cm^{-1}.

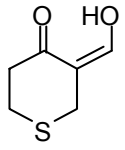
^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.40 (2H, ap t, *J* = 1.5 Hz, HC-5), 2.80 (2H, ap t, *J* = 6 Hz, H_2C-7), 2.51 (2H, ap ddt, *J* = 1.5, 1.5, 6 Hz, H_2C-8), 1.69 (6H, brs, H_3C x 2).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.1, 161.2, 105.7, 102.2, 29.5, 25.3, 24.6, 23.1

LRMS (EI), *m/z* (relative intensity): 200 ($[M]^+$, 43), 142 (100), 114 (76), 98 (1), 85 (29), 59 (3), 57 (17), 55 (10).

HRMS *m/z* calcd. for $C_9H_{12}O_3S$: 200.0507; found: 200.0509.

(*E*)-3-(Hydroxymethylene)dihydro-2*H*-thiopyran-4(3*H*)-one

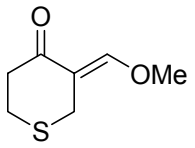


156

To a stirred solution of **119** (3.2 g, 17.0 mmol) in acetone (110 mL) was added 6 M HCl (80 mL) at rt. The reaction mixture was allowed to stir for 2 h, extracted with CH_2Cl_2 (150 mL x 3) and the organic layers concentrated. The residue was dissolved in CH_2Cl_2 (100 mL), extracted with 2 N NaOH (20 mL x 3) and the combined aqueous layers were acidified to pH 1 (Note: ice was added to prevent the temperature from rising above 0 ^oC; **156** decomposes rapidly at rt). The acidified mixture was extracted with CH_2Cl_2, dried over Na_2SO_4 and concentrated without heating to afforded the titled compound (2.44 g, >90% by quantitative internal standard).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 13.38 (1H, br s, OH), 2.72 (1H, br s, HC=), 2.16 (2H, br s, HC-2), 1.58 (2H, t, 6.5 Hz, HC-5), 1.44, (2H, t, 6.5 Hz, HC-6).

(Z)-Tetrahydro-3-(methoxymethylene)thiopyran-4-one



157

To a stirred solution of **156** (0.831 g, 5.76 mmol) in dry acetone (10 mL) was added K_2CO_3 (1.2 g, 8.68 mmol) at r.t under argon. After 2 min, Me_2SO_4 (0.60 mL, 6.34 mmol) was added and the mixture stirred vigorously for 5 h at the same temperature. The reaction was filtered through celite, concentrated and fractionated on deactivated silica gel (5% V/W Et_3N/ silica gel) using EtOAc:hex (1:4) to afford a viscous oil that was > 95% pure by NMR (820 mg, 90% by quantitative internal standard).

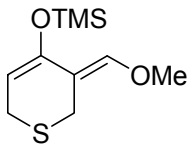
IR (DRIFT) ν_{max}: 2935, 1673, 1591, 1439, 1248, 1135, 1071 cm^{-1}.

^{1}H NMR (500 MHz, C_6D_6) δ: 7.21 (1H, br s, = CH), 3.50 (2H, br s, H_2C-2), 2.98 (3H, br s, OCH_3), 2.54 (2H, t, *J* = 6.5 Hz, HC-5), 2.44 (2H, t, *J* = 6.5 Hz, HC-6).

^{13}C NMR (125 MHz, C_6D_6) δ: 195.9, 156.7, 114.8, 61.1, 33.9, 26.6, 25.1.

LRMS (EI), *m/z* (relative intensity): 158 ($[100]^+$, M), 130 (16), 102 (32), 73 (11), 69 (20), 57 (9), 54 (24).
HRMS *m/z* calcd. for $C_7H_{10}O_2S$: 158.0402; found: 158.0401.

((3Z)-3,6-Dihydro-3-(methoxymethylene)-2H-thiopyran-4-yloxy)trimethylsilane.



158

Prepared according to published procedure; [143]

To a stirred solution of **157** (568 mg, 3.59 mmol) in dry CH_2Cl_2 (10 mL) was added Et_3N (1.50 mL, 10.76 mmol), TMSCl (1.37 mL, 0.76 mmol) and $ZnCl_2$ (98 mg, 0.72 mmol) sequentially under argon. The reaction mixture was stirred for 24 h, concentrated and re-suspended in hexanes. The suspension was filtered through celite and Na_2SO_4 and the residue washed with hexanes. The combined filtrates were concentrated to give a light brownish yellow oil that was used without any further purification > 90% by quantitative internal standard (810 mg).

IR (DRIFT) ν_{max}: 2948, 2834, 1711, 1648, 1420, 1236, 1135, 868 cm^{-1}.

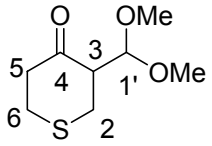
^{1}H NMR (500 MHz, C_6D_6) δ: 6.44 (1H, br s, HC=), 4.95 (1H, t, *J* = 4.5 Hz, HC-5), 3.58 (2H, br s, HC-2), 3.11 (3H, br s, OCH_3), 3.06 (2H, d, *J* = 4.5 Hz, HC-6), 0.17 (9H, br s, $Si(CH_3)_3$).

^{13}C NMR (125 MHz, C_6D_6) δ: 149.2, 144.9, 111.2, 102.9, 60.2, 26.3, 24.8, 0.7.

LRMS (EI), *m/z* (relative intensity): 230 ($[M]^+$, 16), 158 (62), 147 (18), 130 (14), 125 (11), 102 (25), 84 (100), 73 (57).

HRMS *m/z* calcd. for $C_{10}H_{18}O_2SSi$: 230.0797; found: 230.0804.

Tetrahydro-3-(dimethoxymethyl)thiopyran-4-one



159

p-TsOH (105 mg, 0.55 mmol) was added to a solution of keto enol **156** (156 mg, 1.01 mmol) in a mixture of benzene (20 mL) and MeOH (15 mL). After heating under reflux for 3 h, the mixture was concentrated. The residue was taken up in CH_2Cl_2, washed with $NaHCO_3$, dried over Na_2SO_4, concentrated and a portion of it (25 mg) fractionated by PTLC (50% EtOAc in Hexanes) to afford the titled compound (9 mg, 5%, based on starting material).

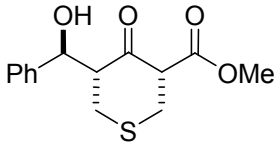
^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.08 (1H, d, *J* = 6.5 Hz, HC-1'), 3.24 (3H, br s, OCH_3), 3.23 (3H, br s, OCH3), 3.00-2.84 (3H, m), 2.46-2.27 (4H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 207.7, 102.6, 55.8, 54.9, 54.7, 43.9, 31.6, 30.9.

LRMS (EI), *m/z* (relative intensity): 190 ($[M]^+$, 2), 102 (7), 84 (60), 75 (100), 71 (34).

HRMS *m/z* calcd. for $C_8H_{14}O_3S$: 190.0664; found: 190.0667.

Methyl (5S)-tetrahydro-5-((S)-hydroxy(phenyl)methyl)-4-oxo-2H-thiopyran-3-carboxylate



161as

To a stirred solution of freshly prepared LDA in THF (20 mL) at -78 °C (DIPA, 3.0 mL, 21 mmol; n-BuLi, 7.8 mL, 19 mmol, [2.48 M]) was added dropwise the keto ester **124** (1.13 g, 6.48 mmol) in THF (5 mL) over 2min. After 30 mins, benzaldehyde (0.73 mL, 7 mmol) was added over 30 sec. The reaction was quenched with a (sat) solution of NH_4Cl (30 mL) after 1 min, warmed up to rt and extracted with EtOAc (50 mL x 3). The combined organic phase was dried (Na_2SO_4), concentrated and fractionated using silica gel (20% EtOAc in hexanes) to give aldol adducts (1.2 g, 65% combined yield in 8:1 ratio favoring the anti adducts). The mixture of the anti diastereoisomers was subjected to crystallization (20% EtOAc in hexanes) to afford the titled compound as white crystals (946 mg, 51%, mp 143-145 ^{o}C).

IR (DRIFT) ν_{max}: 3550, 1738, 1702, 1432, 1343, 1253, 1157, 703 cm^{-1}.

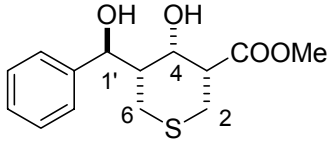
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.41-7.31 (5H, m, Ar), 4.89 (1H, d, *J* = 8.5 Hz, HC-1'), 3.85 (1H, dd, *J* = 5, 12 Hz, HC-3), 3.81 (3H, brs, OCH_3), 3.29 (1H, dd, *J* = 12, 13.5 Hz, HC-2), 3.12 (1H, ddd, *J* = 5, 8.5, 12 Hz, HC-5), 3.05 (1H, ddd, *J* = 3, 5, 13.5 Hz, HC-2), 2.65 (1H, dd, *J* = 12, 13.5 Hz, HC-6), 2.40 (1H, ddd, *J* = 3, 5, 13.5 Hz, HC-6).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 207.6, 169.0, 139.9, 129.0, 128.7, 127.2, 73.6, 60.7, 60.5, 52.7, 33.7, 33.4.

LRMS (EI), *m/z* (relative intensity): 280 ($[M]^+$, 1), 233 (6), 174 (88), 141 (30), 114 (69), 107 (36), 79 (100), 54 (55).

HRMS *m/z* calcd.for $C_{14}H_{16}O_4S$: 280.0769; found: 280.0774.

Methyl (3R,4S,5S)-tetrahydro-4-hydroxy-5-((S)-hydroxy(phenyl)methyl)-2H-thiopyran-3-carboxylate.



163ass

Prepared according to published procedure;[145]

To a stirred solution of the aldol **161as** (51 mg, 0.18 mmol) under argon at 0 °C in a mixture of MeCN (1 mL) and AcOH (1 mL) was added $NaBH(OAc)_3$ (193 mg, 0.91 mmol) in one portion. After 5.5 h at the same temperature, sat. sodium potassium tatrate (4 mL) was added and the reaction was removed from the ice bath and stirred at r.t for 30 mins. The mixture was diluted with EtOAc (10 mL) and washed with $NaHCO_3$ (5 mL x 2). The organic phase was dried, concentrated and crystallized from EtOAc/hexanes (1/4 v/v) to give the titled compound (47.8 mg, 93% yield).

IR (DRIFT) ν_{max}: 3454, 2922, 1720, 1432, 1259, 1169, 1014, 697 cm^{-1}.

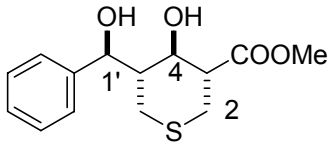
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.33 (5H, m, Ph), 4.76 (1H, d, *J* = 6 Hz, HC-1'), 4.45 (1H, dd, *J* = 1.5, 2 Hz, HC-4), 3.69 (3H, br s, OCH_3), 3.18 (1H, dd, *J* = 3,12 Hz, HC-6ax), 3.13 (1H, dd, *J* = 3,12 Hz, HC-2ax), 2.65 (1H, ddd, *J* = 1.5,3,12 Hz, HC-3), 2.53 (1H, m, HC-6eq), 2.11 (1H, m, HC-2eq), 2.02 (1H, dddd, *J* = 2,3,6,12 Hz, HC-5).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.1, 142.4, 128.4, 127.6, 126.0, 76.1, 64.8, 52.1, 48.7, 48.5, 24.3, 23.3.

LRMS (EI), *m/z* (relative intensity): 282 ($[M]^+$, 10), 175 (26), 158 (100), 117 (16), 115 (13), 107 (19), 98 (59), 79 (22).

HRMS *m/z* calcd. for $C_{14}H_{18}O_4S$: 282.0926; found: 282.0925.

Methyl (3*R*,4*R*,5*S*)-tetrahydro-4-hydroxy-5-((*S*)-hydroxy(phenyl)methyl)-2H-thiopyran-3-carboxylate



163aaa

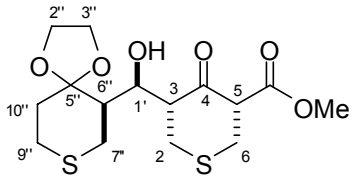
Prepared according to published procedure;[148,149]

To a stirred solution of the aldol **161as** (27 mg, 0.10 mmol) under argon at -78 ^oC in a mixture of THF (1.2 mL) and MeOH (0.2 mL) was added Et_2BOMe (15 µL, 0.12 mmol) and the mixture warmed up to rt over 30 mins. The mixture was cooled to -78 ^oC for 5 min, $NaBH_4$ (3 mg, 0.77 mmol) was added in one portion, and the mixture stirred at the same temp for 5 h. Sat. sodium potassium tatrate (4 mL) was added, the cold bath removed and the mixture stirred at rt for 4 h. The mixture was extracted with EtOAc (10 mL), the combined organic phase was dried, concentrated and fractionated to give the titled compound **163aaa** (22 mg, 80%) and **163ass** (2.5 mg, 10%).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.40-7.31 (5H, m, Ar), 4.77 (1H, d, *J* = 7.5 Hz, HC-1'), 3.90 (1H, dd, *J* = 9.5, 9.5 Hz, HC-4), 3.78 (3H, br s, OCH_3), 2.88-2.78 (2H, m), 2.68 (1H, dd, *J* = 12.5, 13.5 Hz), 2.22-2.15 (2H, m), 2.11-2.04 (1H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 174.1, 141.5, 128.9, 128.6, 127.4, 79.4, 52.6, 52.4, 50.2, 30.0, 29.4.

Methyl 3-[(1,4-Dioxa-8-thia-spiro[4.5]dec-6-yl)-hydroxymethyl]-tetrahydro-thiopyran-4-one-5-carboxylate.



168as

To a stirred solution of freshly prepared LDA in THF (20 mL) at -78 ^{o}C (DIPA, 1.45 mL, 10.4 mmol; n-BuLI, 8.9 mL, 9.7 mmol) was added dropwise the keto ester **124** (677 mg, 3.89 mmol) in THF(10 mL) over 3 min. The mixture was stirred for 45 min at the same temperature and aldehyde **119** (610 mg, 3.24 mmol) in THF (5 mL) was added over 1 min. The mixture was quenched with NH_4Cl after 20 min, warmed up to rt, diluted with brine, and extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), concentrated and fractionated on silica gel (25% EtOAc in hexanes) to afford **168** as a mixture of 4 diastereomers (852 mg, 72%). The mixture was allowed to stand in a mixture of EtOAC: hexanes (1:3) to afford the title compound as a light yellow precipitate (395 mg, 33%).

IR (DRIFT) v_{max}: 3493, 2910, 1743, 1718, 1426, 1331, 1261, 1160 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.28 (1H, dd, *J* = 4,7, Hz, HC-1'), 3.94-3.88 (4H, m, HC-2'',2'',3'',3''), 3.87 (1H, dd, *J* = 4.5,12, Hz, HC-5), 3.75 (3H, br s, OCH_3), 3.32 (1H, ddd, *J* = 4,4,12, Hz, HC-3), 3.29 (1H, dd, *J* = 12,13.5, Hz, HC-6ax), 3.20 (1H, dd, *J* = 13.5,13.5, Hz, HC-2ax), 3.07-3.01 (2H, m, HC-7''ax, 2eq), 2.94 (1H, ddd, *J* = 1,7,13.5, Hz, HC-7'' eq), 2.91 (1H, ddd, *J* = 3.5,4.5,13.5, Hz, HC-6eq),

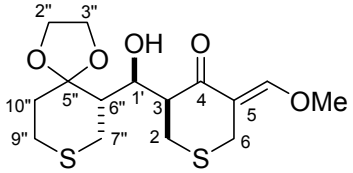
2.84 (1H, ddd, *J* = 3.5,9.5,13, Hz, HC-9"ax), 2.55 (1H, m, HC-9eq), 2.16 (1H, ddd, *J* = 3.5,7,9.5, Hz, HC-6"), 1.83 (1H, ddd, *J* = 3.5,9.5,13.5, Hz, HC-10"), 1.75 (1H, ddd, *J* = 3.5,6.5,13.5, Hz, HC-10").

^{13}C NMR (125 MHz, $CDCl_3$) δ: 208.6 (C-4), 168.9 (COOMe), 108.8 (C-5"), 70.3 (C-1'), 65.1 (C-2" or C-3"), 64.3 (C-3" or C-2"), 60.8 (C-5), 56.7 (C-3), 52.4 (OCH_3), 47.2 (C-6"), 34.1 (C-2), 29.0 (C-7"), 26.8 (C-9").

LRMS (EI), *m/z* (relative intensity): 362 ($[M]^+$ 5), 344 (5), 300 (13), 159 (25), 132 (70), 115 (11), 99 (100), 86 (16).

HRMS *m/z* calcd for $C_{15}H_{22}O_6S_2$ 362.4616 found 362.0858.

3-[(1,4-Dioxa-8-thia-spiro[4.5]dec-6-yl)-hydroxy-methyl]-5-methoxymethylene-tetrahydro-thiopyran-4-one



170sa

$MgBr_2.Et_2O$ (1.04 g, 4.02 mmol) was added in one portion to a stirred solution of aldehyde **119** (252 mg, 1.34 mmol) in CH_2Cl_2 (4.8 mL) at 0 ^oC under argon. After 15 min, a solution of the TMS ether **158** (580 mg, 2.52 mmol) in CH_2Cl_2 (2 mL) was added dropwise. The reaction mixture was stirred vigorously from 40 min and then was poured into phosphate buffer pH 7 (5 mL) at 0 ^oC. The organic phase was separated and the aqueous phase extracted twice with 10 mL CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), concentrated and fractionated on deactivated silica gel (5% V/W Et_3N/ silica gel) using EtOAc:Hex (1:2) to afford the titled compound as a solid (242 mg, 52%) and the *anti-anti* diastereomer **170aa** (161 mg, 35%).

Alternate method

A solution of Et_2AlCl (0.45 mL, 0.90 mmol) in CH_2Cl_2 (2 M solution) was added to a solution of the aldehyde **119** (68 mg, 0.36 mmol) in a CH_2Cl_2 (2 mL) at -78 ^oC. After 2 min, a solution of the TMS ether **158** (125 mg, 0.54 mmol) in CH_2Cl_2 (0.5 mL) was added and the mixture stirred at the same temp for 1 h. The reaction mixture was poured into phosphate buffer pH 7 (5 mL) at 0 ^oC, the organic phase separated and the aqueous phase extracted twice with 10 mL CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), concentrated and fractionated on deactivated silica gel (5% V/W Et_3N/ silica gel) using EtOAc:Hex (1:2) to afford the titled compound (30 mg, 24%) and the *anti-anti* diastereomer **170aa** (161 mg, 16%).

Using Me_2AlCl under same condition and scale gave a much lower yield of the same ratio of products. 26% total yield of 1.5:1 ratio of products.

IR (DRIFT) ν_{max}: 3482, 2927, 1666, 1586, 1424, 1246, 1138, 1101 cm^{-1}.

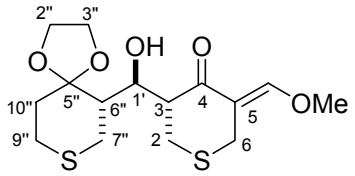
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.33 (1H, br s, = HC), 4.84 (1H, dd, *J* = 2,9.5 Hz, HC-1'), 4.07-3.97 (5H, m, HC-2",2",3",3", OH), 3.87 (3H, br s, OCH_3), 3.50 (2H, br s, HC-6, 6), 3.26 (1H, dd, *J* = 13.5,13.5 Hz, HC-2ax), 2.79-2.59 (6H, m, HC-9",9",7",7",3,2), 2.20 (1H, ddd, *J* = 3.5,7.5,13.5 Hz, HC-10"), 2.04 (1H, ddd, *J* = 3.5,9,13 Hz, HC-6"), 1.82 (1H, ddd, *J* = 3.5,9,13.5 Hz, HC-10").

^{13}C NMR (125 MHz, $CDCl_3$) δ: 190.49 (C-4), 157.72 (CH=), 114.85 (C-5), 110.93 (C-5"), 71.28 (C-1'), 65.00 (C-2" or C-3"), 64.20 (C-3" or C-2"), 62.05 (OCH_3), 51.22 (C-3), 47.41 (C-6"), 35.09 (C-10"), 29.04 9 (C-7"), 26.79 (C-9"), 25.52 (C-2), 25.09 (C-6).

LRMS (EI), *m/z* (relative intensity): 346 (6 $[M]^+$), 328 (7), 158 (41), 131 (42), 99 (100), 86 (22), 69 (10), 54 (20).

HRMS *m/z* calcd for $C_{15}H_{22}O_5S_2$ 346.0909, found 346.0910.

3-[(1,4-Dioxa-8-thia-spiro[4.5]dec-6-yl)-hydroxy-methyl]-5-methoxymethylene-tetrahydro-thiopyran-4-one.



170aa

IR (DRIFT) ν_{max}: 3493, 2922, 1666, 1586, 1424, 1327, 1241, 1138 cm^{-1}

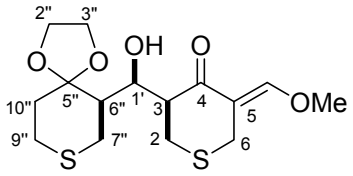
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.28 (1H, dd, *J* = 1,1 Hz, HC=), 4.29 (1H, ddd, *J* = 2,2,8.5 Hz, HC-1'), 4.07-3.98 (5H, m, HC-2",2",3",3",OH), 3.87 (3H, br s, OCH_3), 3.49 (2H, br s, HC-6,6), 3.22 (1H, dd, *J* = 11,13.5 Hz, HC-2ax), 2.94-2.66 (6H, m, HC-2,3,7",7",9",9"), 2.53 (1H, ddd, *J* = 3,7,8.5, Hz, HC-6"), 2.16 (1H, ddd, *J* = 4,9,13.5 Hz HC-10"), 1.81 (1H, ddd, *J* = 3.5,7.5,13.5, Hz, HC-10").

^{13}C NMR (125 MHz, $CDCl_3$) δ: 198.4 (C-4), 157.6 (=CH), 115.5 (C-5), 110.9 (C-5"), 74.0 (C-1'), 64.9 (C-2" or C-3"), 64.3 (C-3" or C-2"), 62.1 (OCH_3), 50.6 (C-3), 47.4 (C-6"), 34.5 (C-10"), 30.5 (C-2), 30.1 (C-7"), 27.0 (C-9"), 25.1 (C-6).

LRMS (EI), *m/z* (relative intensity): 346 ($[M]^+$ 12), 266 (6), 188 (13), 158 (48), 132 (40), 99 (100), 86 (24), 54 (40).

HRMS *m/z* calcd for $C_{15}H_{22}O_5S_2$ 346.0909 found 346.0908.

3-[(1,4-Dioxa-8-thia-spiro[4.5]dec-6-yl)-hydroxy-methyl]-5-methoxymethylene-tetrahydro-thiopyran-4-one(170ss)



170ss

Method 1

A solution of $SnCl_4$ (0.035 mL, 0.299 mmol) in CH_2Cl_2 (1.5 mL) was added to a solution of the aldehyde **119** (51.0 mg, 0.270 mmol) in a CH_2Cl_2 (1 mL) at -78 ^oC under argon. After 20 mins, a solution of the TMS ether **158** (125 mg, 0.544 mmol) in CH_2Cl_2 (0.7 mL) was added and the mixture stirred at the same temparature for 2 h. The reaction mixture was poured into phosphate buffer pH 7 (5 mL) at 0 ^oC, the organic phase separated and the aqueous phase extracted twice with 10 mL CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), concentrated and fractionated on deactivated silica gel (5% V/W Et_3N/ silica gel) using EtOAc:Hex (1:2) to afford the titled compound (47 mg, 50%) and the *ant-syn* diastereomer **170as** (3 mg, 3%).

Method 2

A solution of $TiCl_4$ (0.113 mL, 1.03 mmol) in CH_2Cl_2 (0.75 mL) was added to the solution of the ketone **157** (148 mg, 0.936 mmol) in CH_2Cl_2 (2.5 mL) at -78 °C under argon to give a fine orange slurry. After 40 mins, (-)-sparteine (258 mg, 1.12 mmol) in CH_2Cl_2 (1.5 mL) was added giving a deep red solution that was allowed to stir for 1 h. A solution of the aldehyde **119** (88 mg, 0.468 mmol) in CH_2Cl_2 (2 mL) was added to the mixture and the reaction stirred for another 1h. The reaction mixture was poured into phosphate buffer pH 7 (5 mL) at 0 ^oC, the

organic phase separated and the aqueous phase extracted twice with 10 mL CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), concentrated and fractionated on deactivated silica gel (5% V/W Et_3N/ silica gel) using EtOAc:Hex (1:2) to afford **170ss** and **170as** (123mg, 76% combined yield, 7:1, **170ss**:**17as**).

Method 3

A solution of the ketone **157** (148 mg, 0.936 mmol) in CH_2Cl_2 (1 mL) was added to a suspension of $Sn(OTf)_2$ (89 mg, 0.213 mmol) in CH_2Cl_2 (2 mL) at -78 °C under argon. After 2 mins, Et_3N (0.036 mL, 0.255 mmol) was added and the mixture allowed to stir for 4 h. A solution of the aldehyde **119** (40 mg, 0.170 mmol) in CH_2Cl_2 (1 mL) was added to the mixture and the reaction stirred for another 5 h. The reaction mixture was poured into phosphate buffer pH 7 (5 mL) at 0 °C, the organic phase separated and the aqueous phase extracted twice with 10 mL CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), concentrated and fractionated on deactivated silica gel (5% V/W Et_3N/ silica gel) using EtOAc:Hex (1:2) to afford the titled compound as a solid (44 mg, 50%).

IR (DRIFT) ν_{max}: 3484, 2935, 1667, 1585, 1420, 1248, 1141, 900 cm^{-1}.

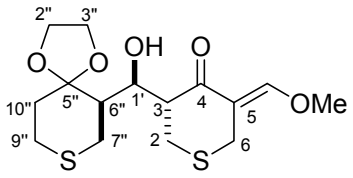
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.23 (1H br s HC=), 4.71 (1H ddd *J* = 3,4,7.5 ,Hz, HC-1'), 4.05-3.94 (4H m HC-2",2",3",3"), 3.86 (3H br s OCH_3), 3.48 (2H br s HC-6,6) 3.09-2.88 (6H m HC-2,2,3,7",7",OH) 2.75 (1H ddd 3, *J* = 10.5,13.5 Hz, HC-9"ax), 2.59 (1H dddd *J* = 1.5,3.5,6,13.5 Hz, HC-9"eq), 2.15 (1H ddd, *J* = 4,4,9.5 Hz, HC-6") 2.08 (1H ddd *J* = 3,6,14 Hz, HC-10"), 1.73 (1H ddd, *J* = 3.5,10.5,14 Hz, HC-10").

^{13}C NMR (125 MHz, $CDCl_3$) δ: 199.5 (C= O) 157.5(= CH), 114.6(C-5), 110.0(C-5"), 67.5(C-1'), 64.7(C-2" or C-3") 64.6(C-3" or C-2"), 62.2(OCH_3), 52.3(C-3) 46.7(C-6"), 35.8(C-10"), 27.5(C-7"), 26.8(C-9"), 26.6(C-2), 23.5(C-6).

LRMS (EI), *m/z* (relative intensity): 346([M]$^+$ 7), 187(8), 158(38), 133(15), 131(37), 125(11), 99(100), 86(11).

HRMS *m/z* calcd for $C_{15}H_{22}O_5S_2$ 346.0909 found 346.0916.

3-[(1,4-Dioxa-8-thia-spiro[4.5]dec-6-yl)-hydroxy-methyl]-5-methoxymethylene-tetrahydro-thiopyran-4-one



170as

Chlorodicyclohexylborane (2.73 mL, 2.73 mmol, 1M solution in Hexanes) was added to a stirred solution of Et_3N (0.418 mL, 2.73 mmol) in CH_2Cl_2 (3.6 mL) at -40 °C under argon. After 2 min, a solution of **157** (431 mg, 2.73 mmol) in CH_2Cl_2 (5 mL) was added dropwise and the mixture stirred for 1 h at the same temperature. The reaction mixture was then cooled to -78 °C for 10 mins and a CH_2Cl_2 (5 mL) solution of the aldehyde **119** (412 mg, 2.19 mmol) was added. After 7 h at -78 °C, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 10 mL), MeOH (5 mL) and 30% aqueous H_2O_2 (3 mL). The mixture was vigorously stirred at 0 °C (ice-bath) for 10 min and then the excess peroxide was destroyed by addition of sat. aqueous Na_2SO_3 (10 mL). The reaction mixture was diluted with brine (10 mL) and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (25% ethyl acetate in hexane) to give a 12:1 ratio of **170as** : **170ss** as a solid (582 mg, 77% yield).

IR (DRIFT) ν_{max}: 3493, 2929, 1673, 1591, 1420, 1248, 1141, 1096 cm^{-1}.

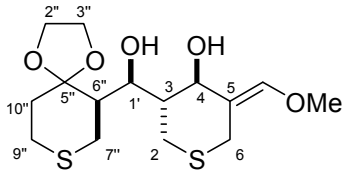
^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.34 (1H, ddd, *J* = 4.5,5,6 Hz, HC-1'), 4.06-3.92 (4H, m, HC-2'',2'',3'',3''), 3.89 (3H, br s, OCH_3), 3.52 (2H, br s, HC-6), 3.45 (1H, d, *J* = 6 Hz, OH), 3.09-3.02 (3H, m, HC-2,3,7''eq), 2.91 (1H, dd, *J* = 9,12, Hz, HC-7''ax), 2.86 (1H, ddd, *J* = 2,3,14 Hz, HC-2eq), 2.80 (1H, ddd, *J* = 3,10.5,13.5 Hz, HC-9''ax), 2.66 (1H, dddd, *J* = 1.5,3.5,6,13.5 Hz, HC-9''eq).

^{13}C NMR (500 MHz, $CDCl_3$) δ: 200.8 (C-4), 157.2 (= CH), 115.0 (C-5), 109.5 (C-5''), 70.1 (C-1'), 64.8 (C-2'' or C-3''), 64.7 (C-3'' or C-2''), 62.3 (OCH_3), 51.1 (C-3), 47.8 (C-6''), 36.3 (C-10''), 28.2 (C-2), 27.8 (C-7''), 26.9 (C-9''), 22.8 (C-6).

LRMS (EI), *m/z* (relative intensity): 346 ($[M]^+$ 3), 270 (4), 188 (5), 158 (13), 132 (37), 115 (6), 99 (100), 86 (17).

HRMS *m/z* calcd for $C_{15}H_{22}O_5S_2$ 346.0909 found 346.0912.

3-[(1,4-Dioxa-8-thia-spiro[4.5]dec-6-yl)-hydroxy-methyl]-5-methoxymethylene-tetrahydro-thiopyran-4-ol.



181as

Et_2BOMe (0.19 mL, 1.58 mmol) was added to a solution of **170as** (417 mg, 1.21mmol) in a mixture of THF (15 mL) and MeOH (3 mL) at -78 °C. The reaction mixture was removed from the dry ice bath for 5 mins and then returned to stir for 30 mins. $NaBH_4$ (77 mg, 2.05 mmol) was added in one portion. The mixture was stirred at -78 °C for 30mins and quenched by addition of 2M NaOH (10 mL). The reaction mixture was allowed to warm to room temperature, diluted with brine (10 mL), and extracted with CH_2Cl_2. The combined organic layers

were dried over Na_2SO_4, concentrated, and fractionated on deactivated silica gel (5% V/W Et_3N/ silica gel) using EtOAc:hex (75% ethyl acetate in hexane) to give the titled compound as a white solid (370 mg, 88%).

IR (DRIFT) ν_{max}: 3452, 2933, 2838, 1669, 1430, 1252, 1240, 1108 cm^{-1}.

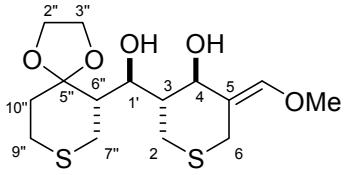
^{1}H NMR (500 MHz, C_6D_6) δ: 6.33 (1H, br s, HC=), 4.46 (1H, dd, *J* = 1,9 Hz, HC-1'), 4.35 (1H, d, *J* = 6.5 Hz, HC-4), 3.83 (1H, br s, OH), 3.54 (1H, br s, OH), 3.30 (2H, m, HC-2" or 3"), 3.15-3.11 (2H, m, HC-6 & 2" or 3"), 3.14 (3H, br s, OCH_3), 3.04 (1H, dd, *J* = 11.5,14 Hz, HC-7"ax), 2.76 (1H, m, HC-2), 2.52 (1H, ddd, *J* = 3,12,13.5 Hz, HC-9"), 2.46 (1H, ddd, *J* = 3,3,14 Hz, HC-7"eq), 2.14-2.01 (4H, m, HC-2,3,6",9"), 1.67 (1H, ddd, *J* = 3,5,14 Hz, HC-10"), 1.49 (1H, ddd, *J* = 3.5,12,14 Hz, HC-10").

^{13}C NMR (125 MHz, C_6D_6) δ: 143.3 (CH=), 114.8 (C-5), 110.9 (C-5"), 73.0 (C-4), 72.4 (C-1'), 64.8 (C-2" or C-3"), 64.1 (C-3" or C-2"), 59.6 (OCH_3), 47.8 (C-3), 46.4 (C-6"), 36.4 (C-10"), 28.4 (C-2), 26.9 (C-9"), 26.1 (C-7"), 24.8 (C-6).

LRMS (EI), *m/z* (relative intensity): 348 ($[M]^+$ 4), 30 (12), 253 (10), 189 (14), 132 (32), 117 (14), 99 (100), 54 (19).

HRMS *m/z* calcd for $C_{15}H_{24}O_5S_2$ 348.1065 found 348.1078.

3-[(1,4-Dioxa-8-thia-spiro[4.5]dec-6-yl)-hydroxy-methyl]-5-methoxymethylene-tetrahydro-thiopyran-4-ol.



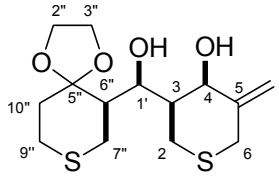
181aa

Et_2BOMe (13 µL, 0.108 mmol) was added to a solution of **170aa** (20 mg, 0.058 mmol) in a mixture of THF (2 mL) and MeOH (0.5 mL) at -78 °C. The reaction mixture was removed from the dry ice bath for 5 mins and then returned to stir for 30 mins. $NaBH_4$ (excess) was added in one portion. The mixture was stirred at -78 °C for 30mins and quenched by addition of water. The reaction mixture was extracted with CH_2Cl_2 (10 mL x 2) and the combined organic layers were concentrated. The residue was dissolved in 2.5% NaOH: MeCN (1:1, v/v) (10 mL) and stirred at room temperature for 1.5 h. The reaction mixture diluted with brine (10 mL), and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated, and fractionated on PTLC using EtOAc:hex (75% ethyl acetate in hexane) to give the titled compound as a white solid (9.6 mg, 46%).

^{1}H NMR (500 MHz, C_6D_6) δ: 6.20 (1H, br s, = CH), 4.40 (1H, ap d, *J* = 7.5 Hz), 4.29 (3H, br s, OCH_3), 4.19 (1H, ap d, *J* = 4.5 Hz), 3.97 (1H, m), 3.82 (1H, d, *J* = 13 Hz), 3.29-3.23 (1H, m), 3.20-3.16 (3H, m), 3.11-3.07 (1H, m), 3.02-3.89 (3H, m), 2.78 (1H, ap d, *J* = 13 Hz), 2.64 (1H, dd, *J* = 9, 13 Hz), 2.41 (1H, ddd, *J* = 3, 10, 13 Hz), 1.71 (1H, ddd, *J* = 3, 7, 13 Hz), 1.43 (1H, ddd, *J* = 3.5, 10, 13.5 Hz).

^{13}C NMR (125 MHz, C_6D_6) δ: 143.0, 115.8, 111.8, 77.9, 72.6, 64.1, 63.8, 59.7, 53.7, 46.6, 35.9, 31.6, 30.3, 26.9, 24.8.

3-[(1,4-Dioxa-8-thia-spiro[4.5]dec-6-yl)-hydroxy-methyl]-5-methylene-tetrahydro-thiopyran-4-ol



182

To a stirred solution of **170ss** (33 mg, 0.10 mmol) in THF (5 mL) at -78 °C under argon was added DIBAL (0.4 mL, 0.4 mmol, 1 M solution in toluene). After stirring for 7 h, 2 M NaOH (2 mL) was added, the bath was removed and the mixture warmed to room temperature. The mixture diluted with brine, extracted with CH_2Cl_2, and fractionated by PTLC (80% EtOAc in hexanes) to afford the titled compound as a white solid (16 mg, 52%)

IR (DRIFT) ν_{max}: 3424, 2916, 1414, 1248, 1090, 1014, 944, 862 cm^{-1}.

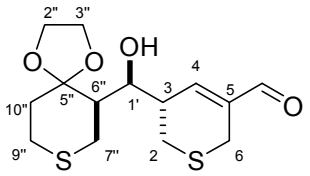
^{1}H NMR (500 MHz, C_6D_6) δ: 4.55 (2H,m, H_2C=), 4.37 (1H, dd, *J* = 3.5,7 Hz, HC-1') 4.06 (1H, br s, HC-4), 3.63 (1H, d, *J* = 13 Hz, HC-6ax), 3.38 (1H, dd, *J* = 11,13 Hz, HC,2ax), 3.29-3.26 (2H, m, HC-2" or 3"), 3.19-3.09 (3H, m, HC-3" or 2", OH), 3.03 (1H, dd, *J* = 10,14 Hz, HC-7"ax), 2.87 (1H, ddd, *J* = 1.5,11,13 Hz, HC-2eq), 2.71 (1H, ddd, *J* = 2,3.5,14 Hz, HC-7"eq), 2.58 (1H, dd, *J* = 1.5, 13 Hz, HC-6eq), 2.51 (1H, ddd, *J* = 3.5, 10.5, 13.5 Hz, HC-9"), 2.34-2.24 (2H, m, HC-3,9"), 2.18 (1H, ddd, *J* = 3.5,3.5,10 Hz, HC-6"), 1.69 (1H, ddd, *J* = 3,6,13.5 Hz, HC-10"), 1.56 (1H, ddd, *J* = 3.5,10.5,13.5 Hz, HC-10"), 1.43 (1H, brs, OH).

^{13}C NMR (125 MHz, C_6D_6) δ: 147.6 (C-5), 110.4 (C-5"), 110.1 (= CH_2), 74.7 (C-4), 71.4 (C-1'), 64.7 (C-2" or C-3"), 64.3 (C-3" or C-2"), 49.9 (C-3), 46.5 (C-6"), 36.4 (C-10"), 30.1 (C-6), 27.5 (C-7" or C-9"), 27.0 (C-9" or C-7"), 25.1 (C-2).

LRMS (EI), *m/z* (relative intensity): 318 ($[M]^+$ 4), 300 (6), 189 (28), 159 (15), 132 (53), 117 (14), 99 (100), 86 (17).

HRMS *m/z* calcd for $C_{14}H_{22}O_4S_2$ 318.0960 found 318.0962.

3-[(1,4-Dioxa-8-thia-spiro[4.5]dec-6-yl)-hydroxy-methyl]-3,6-dihydro-2H-thiopyran-5-carboxylaldehyde



184

$CuCl_2$ (1 mg, catalytic) was added to a stirred solution of **181as** (38 mg, 0.109 mmol) in a mixture of 2-propanol (1.1 mL) and H_2O (0.01 mL, 0.546 mmol) at 50 ^oC. After 2.5 h, the mixture was diluted with CH_2Cl_2 and washed with $NaHCO_3$. The organic phase was dried (Na_2SO_4) and concentrated to give a white solid that was homogeneous by NMR (33 mg, 95%).

Alternative method

p-TsOH (133 mg, 0.77 mmol) was added to a stirred solution of **181as** (702 mg, 2.02 mmol) in wet THF (30 mL) at ambient temp. After 15 min, the mixture was diluted with CH_2Cl_2 and washed with $NaHCO_3$. The organic phase was dried (Na_2SO_4) and concentrated to give a white solid that was homogeneous by NMR (606 mg, 87%).

IR (DRIFT) ν_{max}: 3501, 2905, 1681, 1633, 1424, 1262, 1152, 1100 cm^{-1}.

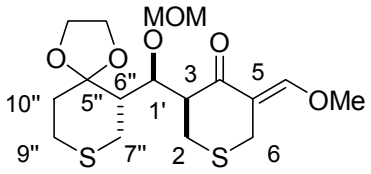
^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.42 (1H, br s, HCO), 7.16 (1H, ddd, *J* = 1.5,1.5,3.5 Hz, HC-4), 4.13-3.98 (5H, m, HC-1',2'',2'',3'',3''), 3.38 (1H, brs, OH), 3.30 (2H, m, HC-6), 3.10 (1H, dd, *J* = 11.5,14 Hz, HC-7''ax), 2.86 (1H, ddd, *J* = 2.5,12,14 Hz, HC-9''), 2.79 (1H, m, HC-3), 2.73-2.67 (2H, m, HC-2, 7''), 2.58 (1H, ddd, *J* = 2.5,7.5,14 Hz, HC-9''), 2.49 (1H, dd, *J* = 8,13.5 Hz, HC-2ax), 2.20 (1H, ddd, *J* = 2.5,4.5,14 Hz, HC-10''), 2.13 (1H, ddd, *J* = 1.5,3.5,11.5 Hz, HC-6''), 1.78 (1H, ddd, *J* = 3.5,12.5,14 Hz, HC-10'').

^{13}C NMR (125 MHz, $CDCl_3$) δ: 193.4, 153.2, 139.3, 110.3, 71.1, 64.9, 64.4, 46.6, 40.1, 36.3, 27.2, 26.7, 25.6, 22.7.

LRMS (EI), *m/z* (relative intensity): 316 ($[M]^+$, 8), 298 (10), 254 (27), 236 (9), 189 (27), 161 (6), 132 (44), 99 (100).

HRMS *m/z* calcd. for $C_{14}H_{20}O_4S_2$: 316.0803; found: 316.0809.

3-[(1,4-Dioxa-8-thia-spiro[4.5]dec-6-yl)-methoxymethoxy-methyl]-5-methoxymethylene-tetrahydro-thiopyran-4-one (190sa).



190sa

DIPEA (0.9 mL, 5.10 mmol) was added to a stirred solution of **170sa** (118 mg, 0.34 mmol) and n-Bu_4NI (36 mg, 0.10 mmol) in CH_2Cl_2 (1 mL) at room temperature under argon. After 2 min, a solution of MOMCl (0.26 mL, 3.41 mmol) was added and reaction mixture stirred vigorously for 24 h at the same temperature. The reaction mixture was poured into a separatory funnel containing 10% HCl (2 mL) and extracted with 10 mL CH_2Cl_2 (x 2). The

combined organic layers was washed with $NaHCO_3$, dried (Na_2SO_4), concentrated, re-suspended in 50% EtOAC: hexanes and then filtered through a short silica pad to afford the titled compound as a flakey crystalline solid (127 mg, 96%).

IR (DRIFT) ν_{max}: 2889, 2823, 1668, 1586, 1443, 1246, 1141, 1052 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.26 (1H, br s, =CH), 5.03 (1H, dd, *J* = 1, 3.5 Hz, HC- 1'), 4.58 (2H, m, OH_2CO), 4.08-3.86 (4H, m, HC-2" & HC-3"), 3.88 (1H, br s, $=OH_3C$), 3.49 (2H, br s, HC-6), 3.32 (3H, br s, $H_2CO\underline{H}_3C$), 3.13-2.86 (6H, m, HC-7",7", 2, 2, 9" & 3), 2.54 (1H, dddd, *J* = 2, 3.5, 3.5, 13 Hz, HC-9"eq), 2.49 (1H, ddd, *J* = 3.5, 3.5, 11.5 Hz, HC-6"), 2.10 (1H, ddd, *J* = 3.5, 3.5, 13 Hz, HC-10"eq), 1.77 (1H, ddd, *J* = 3.5, 13, 13 Hz, HC10"ax).

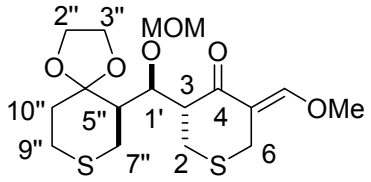
^{13}C NMR (125 MHz, $CDCl_3$) δ: 198.7, (C-4), 157.1 (=CH), 114.8 (C-5), 109.0 (C-5"), 97.4 (OCH_2O), 74.1 (C-1'), 64.8 (C-2" or C-3"), 64.5 (C-3" or C-2"), 62.0 ($CHO\underline{C}H_3$), 56.1 ($CH_2O\underline{C}H_3$), 52.6 (C-3), 51.2 (C-6"), 37.4 (C-10"), 28.6 (C-7"), 27.4 (C-2), 27.2 (C-9"), 24.3 (C-6).

LRMS (EI), *m/z* (relative intensity): 390 ($[M]^+$, 4), 358 (14), 328 (10), 231 (14), 157 (13), 131 (17), 99 (100), 54 (23).

HRMS *m/z* calcd. for $C_{17}H_{26}O_6S_2$: 390.1171; found: 390.1180.

Anal. Calcd for $C_{17}H_{26}O_6S_2$: C, 52.29; H, 6.71. Found: C, 52.44; H, 6.56

3-[(1,4-Dioxa-8-thia-spiro[4.5]dec-6-yl)-methoxymethoxy-methyl]-5-methoxymethylene-tetrahydro-thiopyran-4-one



190as

DIPEA (0.98 mL, 5.59 mmol) was added to a stirred solution of **170as** (218 mg, 0.626 mmol) and n-Bu_4NI (230 mg, 0.631 mmol) in CH_2Cl_2 (1 mL) at room temperature under argon. After 2 min, MOMCl (0.29 mL, 3.75 mmol) was added and reaction mixture stirred vigorously for 24 h at the same temperature. The reaction mixture was poured into a separatory funnel containing 10% HCl (5 mL) and extracted with 10 mL CH_2Cl_2 (x 2). The combined organic layers were washed with $NaHCO_3$, was dried (Na_2SO_4), concentrated, re-suspended in 50% EtOAC: hexanes and then filtered through a short silica pad to afford the titled compound as a light yellow solid (238 mg, 97%).

IR (DRIFT) ν_{max}: 2935, 1673, 1591, 1432, 1236, 1141, 1026 cm^{-1}.

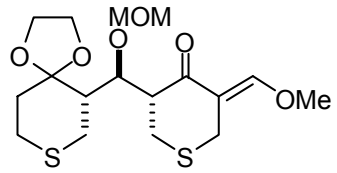
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.24 (1H, dd, *J* = 1,1.5 Hz, = CH), 4.74 (1H, d, *J* = 6.5 Hz, OCH_2O), 4.64 (1H, d, *J* = 6.5 Hz, OCH_2O), 4.54 (1H, dd, *J* = 1.5,7 Hz, HC-1'), 3.98-3.88 (4H, m, HC-2",2",3",3"), 3.86 (3H, br s, OCH_3), 3.56 (1H, ddd, *J* = 1,2.5,15 Hz, HC-6), 3.40 (1H, dd, *J* = 1.5,15 Hz, HC-6), 3.37 (3H, br s, OCH_3), 3.17 (1H, dd, *J* = 11,13 Hz, HC-2ax), 3.30 (1H, ddd, *J* = 1,3,13.5 Hz, HC-7"eq), 3.10 (1H, ddd, *J* = 2.5,7,11 Hz, HC-3), 2.94 (1H, ddd, *J* = 2.5,5,13 Hz, HC-2eq), 2.83 (1H, dd, *J* = 8.5,13.5 Hz, HC-7"ax), 2.73-2.62 (2H, m, HC-9", 9"), 2.35 (1H, ddd, *J* = 3,8,8.5 Hz, HC-6"), 2.12 (1H, ddd, *J* = 3.5,7,13.5 Hz, HC-10"), 1.66 (1H, ddd, *J* = 3.5,9,13.5 Hz, HC-10").

^{13}C NMR (125 MHz, $CDCl_3$) δ: 198.73, 196.7, 156.8, 115.0, 109.1, 97.7, 64.7, 64.0, 61.9, 56.4, 55.9, 48.0, 35.0, 29.4, 28.9, 26.9, 25.0.

LRMS (EI), *m/z* (relative intensity): 390 ($[M]^+$, 2), 358 (30), 328 (6), 266 (12), 159 (13), 131 (30),99 (100).

HRMS *m/z* calcd for $C_{17}H_{26}O_6S_2$ 390.1171, found 390.1180.

3-[(1,4-Dioxa-8-thia-spiro[4.5]dec-6-yl)-methoxymethoxy-methyl]-5-methoxymethylene-tetrahydro-thiopyran-4-one.



190aa

DIPEA (0.66 mL, 3.77 mmol) was added to a stirred solution of **170aa** (85 mg, 0.245 mmol) and n-Bu_4NI (26 mg, 0.071 mmol) in CH_2Cl_2 (1 mL) at room temperature under argon. After 2 min, MOMCl (0.19 mL, 2.50 mmol) was added and reaction mixture stirred vigorously for 24 h at the same temperature. The reaction mixture was poured into a separatory funnel containing 10% HCl (5 mL) and extracted with 10 mL CH_2Cl_2 (x 2). The combined organic layers were washed with $NaHCO_3$, was dried (Na_2SO_4), concentrated, re-suspended in 50% EtOAC: hexanes and then filtered through a short silica pad to afford the titled compound as a light yellow solid (92 mg, 96%).

IR (DRIFT) ν_{max}: 2920, 1672, 1587, 1433, 1245, 1142, 1102, 1034 cm^{-1}.

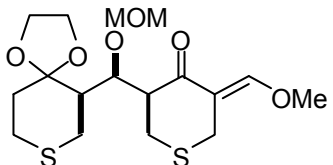
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.27 (1H, br s, HC=), 4.78 (1H, d, *J* = 7 Hz, OCH_2O), 4.68 (1H, d, *J* = 7 Hz, OCH_2O), 4.27 (1H, dd, *J* = 3,5 Hz, HC-1'), 4.02-3.94 (4H, m, HC-2'',2'',3'',3''), 3.87 (3H, br s, OCH_3), 3.53 (1H, ddd, *J* = 1.5, 1.5, 15 Hz, HC-6eq), 3.45 (1H, dd, *J* = 1.5,15 Hz, HC-6ax), 3.35 (3H, br s, OCH_3), 3.17 (1H, ddd, *J* = 3, 5.5, 9.5 Hz, HC-3), 3.09 (1H, dd, *J* = 9.5, 13.5 Hz, HC-2ax), 3.00 (1H, ddd, *J* = 2, 5.5, 13.5 Hz, HC-2eq), 2.91-2.83 (2H, m, HC-7''ax,7''eq), 2.75-2.65 (2H, m, HC-9''ax, 9''eq), 2.38 (1H, ddd, *J* = 3, 5, 11 Hz, HC-6''), 2.14 (1H, ddd, *J* = 4, 7, 13.5 Hz, HC-10''), 1.77 (1H, ddd, *J* = 4, 8.5, 13.5 Hz, HC-10'').

^{13}C NMR (125 MHz, $CDCl_3$) δ: 197, 157.7, 114.5, 109.2, 98.2, 81.3, 64.5, 64.2, 62.1, 56.1, 52.5, 48.9, 35.7, 31.1, 29.6, 27.1, 24.6.

LRMS (EI), *m/z* (relative intensity): 390 ($[M]^+$, 8), 328 (15), 199 (23), 185 (12), 131 (30), 99 (100), 86 (10), 54 (11).

HRMS *m/z* calcd. for $C_{17}H_{26}O_6S_2$: 390.1171; found: 390.1162.

3-[(1,4-Dioxa-8-thia-spiro[4.5]dec-6-yl)-methoxymethoxy-methyl]-5-methoxymethylene-tetrahydro-thiopyran-4-one



190ss

DIPEA (0.82 mL, 4.65 mmol) was added to a stirred solution of **170ss** (106 mg, 0.31 mmol) and n-Bu_4NI (32 mg, 0.09 mmol) in CH_2Cl_2 (1 mL) at room temperature under argon. After 2 min, MOMCl (0.23 mL, 3.02 mmol) was added and reaction mixture stirred vigorously for 24 h at the same temperature. The reaction mixture was poured into a separatory funnel containing 10% HCl (2 mL) and extracted with 10 mL CH_2Cl_2 (x 2). The combined organic layers were

washed with $NaHCO_3$, was dried (Na_2SO_4), concentrated, re-suspended in 50% EtOAC: hexanes and then filtered through a short silica pad to afford the titled compound as a light yellow solid 113 mg, 95%).

IR (DRIFT) v_{max}: 1666, 1586, 1424, 1246, 1133, 1095, 1031 cm^{-1}.

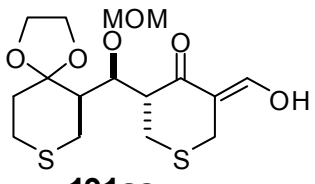
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.27 (1H, br s, HC=), 4.72 (1H, dd, *J* = 1,7.5 Hz, HC-1'), 4.55 (2H, br s, OCH_2O), 4.09-3.95 (4H, m, HC-2'',2'',3'',3''), 3.87 (3H, br s, OCH_3), 3.53 (1H, dd, *J* = 2,15 Hz, HC-6), 3.42 (1H, dd, *J* = 1.5,15 Hz, HC-6), 3.27 (3H, brs, OCH_3), 3.14 (1H, dd, *J* = 11,13 Hz, HC-2ax), 3.01 (1H, ddd, *J* = 1.5,5.5,10.5 Hz, HC-3), 2.94-2.88 (2H, m, HC-7'', 9''), 2.79-2.74 (2H, m, HC-7'', 2eq), 2.63 (1H, m, HC-9''eq), 2.17 (1H, ddd, *J* = 3,7.5,10 Hz, HC-6''), 2.05 (1H, ddd, *J* = 3,5,13.5 Hz, H-10''), 1.71 (1H, ddd, *J* = 3,11,13.5 Hz, H-10'').

^{13}C NMR (125 MHz, $CDCl_3$) δ: 198.2, 157.2, 114.9, 109.1, 98.5, 75.1, 65.2, 64.6, 62.0, 56.5, 55.7, 48.2, 36.1, 29.3, 26.8, 26.5, 25.0.

LRMS (CI, NH_3), *m/z* (relative intensity): 407 ($[M+NH_3]^+$, 6), 390 ($[M]^+$, 7), 342 (77), 330 (44), 312 (100), 204 (44), 131 (49), 99 (94).

HRMS *m/z* calcd. for $C_{17}H_{26}O_6S_2$: 390.5147 (407.1436 $M+NH_3$); found: 407.9948(CI).

3-[(1,4-Dioxa-8-thia-spiro[4.5]dec-6-yl)-methoxymethoxy-methyl]-5-hydroxymethylene-tetrahydro-thiopyran-4-one



191as

To a stirred solution of the MOM protected **180as** (133 mg, 0.34 mmol) in a mixture of THF (5 mL) and H_2O (1 mL) at 0 °C was added TFA (0.30 mL). After 1.5 h at the same temp, the mixture was poured into a separatory funnel containing sat. $NaHCO_3$ (20 mL), diluted with brine (15 mL), and extracted with CH_2Cl_2 (20 mL x 2). The combined organic layers were dried over Na_2SO_4, concentrated, and fractionated on silica gel (33% ethyl acetate in hexane) to give the titled compound as a light pink oil (122 mg, 95%).

IR (DRIFT) ν_{max}: 2923, 1718, 1623, 1572, 1420, 1210, 1090, 1026 cm^{-1}.

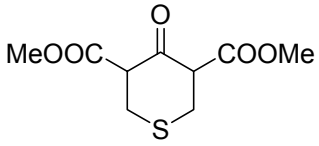
^{1}H NMR (500 MHz, $CDCl_3$) δ: 14.65 (1H, d, *J* = 7 Hz, OH), 7.98 (1H, d, *J* = 7 Hz, HC=), 4.74 (1H, d, *J* = 6.5 Hz, OCH_2O), 4.64 (1H, d, *J* = 6.5 Hz, OCH_2O), 4.40 (1H, dd, *J* = 1.5, 6.5 Hz, HC-1'), 3.99-3.87 (4H, m, HC-2",2",3",3"), 3.51 (1H, d, *J* = 14.5 Hz, HC-6), 3.21 (1H, dd, *J* = 2,14.5 Hz, HC-6), 3.14-3.06 (2H, m, HC-2, 3), 2.99 (1H, ddd, *J* = 1.5, 3.5, 13.5 Hz, HC-7"eq), 2.89 (1H, ddd, *J* = 2.5,3.5,11,5 Hz, HC-2), 2.81 (1H, dd, *J* = 10,13.5 Hz, HC-7"ax), 2.74 (1H, ddd, *J* = 3.5, 10.5, 13.5 Hz, HC-9"ax), 2.61 (1H, dddd, *J* = 1.5, 3.5, 6.5, 13.5 Hz, HC-9"eq), 2.47 (1H, ddd, *J* = 3.5, 6.5, 10 Hz, HC-6"), 2.09 (1H, ddd, *J* = 3.5, 6.5, 13.5 Hz, HC-10eq"), 1.76 (1H, ddd, *J* = 3.5, 10.5, 13.5 Hz, HC-10ax").

^{13}C NMR (125 MHz, $CDCl_3$) δ: 193.9, 175.1, 110.0, 108.9, 97.6, 76.2, 64.7, 64.1, 56.4, 51.8, 48.5, 35.3, 29.1, 28.0, 27.1, 26.8.

LRMS (EI), *m/z* (relative intensity): 376 ($[M]^+$, 1), 344 (27), 314 (13), 252 (13), 159 (15), 132 (50), 99 (100), 54 (9).

HRMS *m/z* calcd. for $C_{16}H_{24}O_6S_2$: 376.1014; found: 376.1018.

Dimethyl tetrahydro-4-oxo-2*H*-thiopyran-3,5-dicarboxylate.[170]



193

A solution of **124** (20.0 g, 0.115 mol) in THF (35 mL) was added dropwise over 5 min to a stirred solution of freshly prepared LDA (DIPA: 48.9 mL, 0.345 mol; n-BuLi: 2.5 M in hexane, 129 mL, 0.32 mol) in THF (200 mL) at -78 °C under argon. After 1 h, methyl chloroformate (8.9 mL, 0.12 mol) was added dropwise over 20 min maintaining the temperature of the reaction mixture below -70 °C. After a further 1 h, the reaction was quenched by addition of saturated aqueous NH_4Cl (300 mL). The mixture was allowed to warm up to room temperature and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4 and concentrated to give a light yellow solid. Trituration of the residue with ether gave the diester **193** as a white solid (19.31 g, 72.4%). Concentration of the ether washings gave a residue that was fractionated by FCC (30% ethyl acetate in hexane) to give additional diester **193** (1.79 g, 6.7%, mp 153-156 °C after recrystallization from $CHCl_3$)

IR (DRIFT) ν_{max}: 3004, 2965, 2928, 1725, 1705, 1434, 1345, 1157 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.59 (0.1H, s, HO (enol)), 3.85-3.75 (1.9H, m, HC-3, HC-5), 3.76 (6H, s, H_3CO), 3.35-3.25 (2H, m, HC-2, HC-6), 3.09-3.00 (2H, m, HC-2, HC-6).

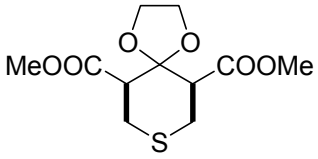
^{13}C NMR (75 MHz, $CDCl_3$) δ: 199.6 (C-4), 168.5 (×2, COO), 59.6 (×2, C-3, C-5), 52.7 (×2, CH_3O), 32.8 (×2, C2, C-6).

LRMS (EI), *m/z* (relative intensity): 232 ([M]$^+$, 42), 200 (41), 173 (92), 140 (40), 113 (30), 85 (26), 73 (12), 54 (100).

HRMS *m/z* calcd for $C_9H_{12}O_5S$ 232.0405, found 232.0409.

Anal. Calcd for $C_9H_{12}O_5S$: C, 46.54; H, 5.21. Found: C, 46.75; H, 5.27.

Dimethyl (6*R*,10*S*)-1,4-dioxa-8-thiaspiro[4.5]decane-6,10-dicarboxylate (*meso*-194c).[170]



meso-**194c**

TMSOTf (1.0 mL, 5.5 mmol) was added to a stirred solution of the ketodiester **193** (2.15 g, 9.27 mmol) in $CHCl_3$ (50 mL) at room temperature under argon. After 5 min, 1,2-bis(trimethylsiloxy)ethane (4.0 mL, 16 mmol) was added and, after stirring for 4 h at room temperature, the mixture was heated under reflux. The reaction was monitored by TLC and after completion (24-48 h), the cooled reaction mixture was poured into a separatory funnel containing saturated aqueous $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with H_2O, dried over Na_2SO_4, concentrated to give a 1.5:1 mixture of (±)-**194** and *meso*-**194c**, respectively (2.17 g, 85%), that was sufficiently pure to be used in the next step. Fractionation of the mixture by FCC (33% ethyl acetate in hexane) gave *meso*-**194c** (0.738 mg, 29%, mp 106-108 °C) and (±)-**194a** (1.30 g, 51%; mp 123-126 °C).

IR (DRIFT) ν_{max}: 2991, 2937, 2905, 1716, 1436, 1349, 1169, 1075 cm^{-1}.

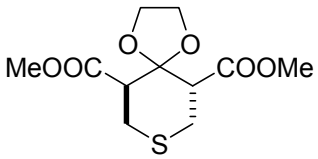
^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.06-4.02 (2H, m, H_2CO), 3.90-3.86 (2H, m, H_2CO), 3.69 (3H, s, H_3CO ×2), 3.32 (2H, dd, *J* = 12.5,14 Hz, HC-7, HC-9), 2.93 (2H, dd, *J* = 3,12.5 Hz, HC-6, HC-10), 2.67-2.60 (2H, m, HC-6, HC-10).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.3 (×2, CO), 108.7 (C-5), 66.7 (×2, CH_2O), 66.6 (×2, CH_2O), 54.2 (×2, C-6, C-10), 52.4 (×2, CH_3O), 29.4 (×2, C-7, C-9).

LRMS (EI), *m/z* (relative intensity): 276 ($[M]^+$, 18), 245 (16), 217 (18), 190 (100), 173 (5), 144 (43), 113 (58), 54 (23).

HRMS *m/z* calcd for $C_{11}H_{16}O_6S$ 276.0668, found 276.0666.

Dimethyl (6*R*,10*R*)-*rel*-1,4-dioxa-8-thiaspiro[4.5]decane-6,10-dicarboxylate ((±)-194a).[170]



(±)-**194a**

IR (DRIFT) ν_{max}: 2954, 2891, 1743, 1435, 1363, 1201, 1167, 1054 cm^{-1}.

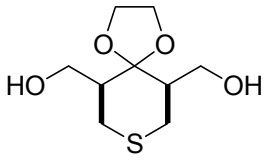
^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.05-3.86 (4H, m, H_2CO × 2), 3.72 (6H, s, H_3CO × 2), 3.39 (2H, dd, *J* = 4, 7.5 Hz, HC-6, HC-10), 3.09 (2H, dd, *J* = 7.5, 14 Hz, HC-7, HC-9), 2.96 (2H, dd, *J* = 4, 14 Hz, HC-7, HC-9).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.3 (× 2, CO), 107.3 (C-5), 65.7 (× 2, CH_2O), 52.2 (× 2, CH_3O), 48.9 (× 2, C-6, C-10), 29.8 (× 2, C-7, C-9).

HRMS *m/z* calcd for $C_{11}H_{16}O_6S$ 276.0668, found 276.0666.

Anal. Calcd for $C_{11}H_{16}O_6S$: C, 47.82; H, 5.84. Found: C, 48.01; H, 5.64.

(6*R*,10*S*)-1,4-Dioxa-8-thiaspiro[4.5]decane-6,10-bismethanol (*meso*-195).[170]



meso **195**

A solution of the *cis* ketaldiester *meso*-**194c** (2.25 g, 8.14 mmol) in THF (15 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (0.62 g, 16 mmol) in THF (70 mL) at 0 °C under argon. The mixture was allowed to warm to room temperature and after 40 min, was quenched by addition of aqueous NaOH (2 N, 15 mL). The mixture was filtered through a short column of Celite® and Na_2SO_4 washing with THF. The combined filtrate and washings were concentrated to give the titled compound as a white solid that was homogeneous by ^{1}H NMR and TLC (1.74 g, 96%; mp 110-113 °C (CH_2Cl_2)).

IR (DRIFT) ν_{max}: 3270, 2953, 2893, 1481, 1236, 1194, 1051 cm^{-1};

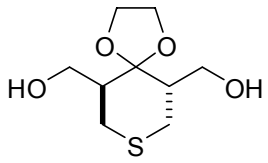
^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.09-4.03 (4H, m, H_2CO × 2), 3.83 (2H, dd, *J* = 5.5, 11 Hz, HCOH × 2), 3.53 (2H, dd, *J* = 6, 11 Hz, HCOH × 2), 2.80-2.69 (4H, m, H_2C-7, H_2C-9), 2.23-2.17 (2H, m, HC-6, HC-10), 2.04 (2H, br s, HO × 2);

^{13}C NMR (125 MHz, $CDCl_3$) δ: 112.3 (C-5), 67.0 (CH_2O), 66.4 (CH_2O), 62.5 (×2, CH_2OH), 51.1 (×2, C-6, C-10), 29.4 (×2, C-7, C-9);

LRMS (EI), *m/z* (relative intensity): 220 ([M]$^+$, 6), 162 (39), 129 (12), 116 (10), 115 (100), 99 (14), 54 (5);

HRMS *m/z* calcd for $C_9H_{16}O_4S$ 220.0769, found 220.0778.

(6*R*,10*R*)-*rel*-1,4-Dioxa-8-thiaspiro[4.5]decane-6,10-bismethanol ((±)-195a).[170]



(±)-**195a**

A solution of (±)-**194a** (1.54 g, 5.57 mmol) in THF (10 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (0.423 g, 11.1 mmol) in THF (40 mL) at 0 °C under argon. The mixture was allowed to warm to room temperature and after 40 min, was quenched by addition of aqueous NaOH (2 N, 15 mL). The mixture was filtered through a short column of Celite® and Na_2SO_4 washing with THF. The combined filtrate and washings were concentrated to give the titled compound as a viscous colorless oil that was homogeneous by ^{1}H NMR and TLC (1.10 g, 90%).

IR (DRIFT) ν_{max}: 3348, 2959, 2881, 1703, 1428, 1266, 1141, 1039 cm^{-1};

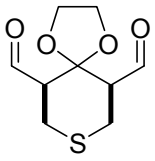
^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.09-4.00 (4H, m, H_2CO × 2), 3.92 (2H, dd, *J* = 6, 11 Hz, HCOH × 2), 3.73 (2H, dd, *J* = 5.5, 11 Hz, HCOH × 2), 2.85-2.70 (4H, m, H_2C-7, H_2C-9), 2.27 (2H, br s, HO × 2), 2.22 (2H, m, HC-6, HC-10);

^{13}C NMR (125 MHz, $CDCl_3$) δ: 111.7 (C-5), 64.9 (× 2, CH_2O), 62.2 (× 2, CH_2OH), 43.9 (× 2, C-6, C-10), 29.3 (× 2, C-7, C-9);

LRMS (EI), *m/z* (relative intensity): 220 ([M]$^+$, 9), 162 (38), 129 (11), 116 (10), 115 (100), 99 (14), 71 (5), 54 (10);

HRMS *m/z* calcd for $C_9H_{16}O_4S$ 220.0769, found 220.0769.

(6*R*,10*S*)-1,4-Dioxa-8-thiaspiro[4.5]decane-6,10-dicarboxaldehyde (*meso*-196).[170]



meso **196**

DMSO (0.93 mL, 13 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (0.57 mL, 6.5 mmol) in CH_2Cl_2 (60 mL) at -78 °C under argon. After 30 min, a warm solution (required to dissolve the diol) of *meso*-**195** (0.68 g, 3.1 mmol) and Me_2S (0.91 mL, 12 mmol) in CH_2Cl_2 (50 mL) was added. After 1.5 h, *i*-Pr_2EtN (3.24 mL, 18.6 mmol) was added, and the reaction mixture was allowed to warm to 0 °C over 20 min. Hexane (50 mL) and toluene (50 mL) were added and reaction mixture was concentrated to a volume of ca. 50 mL. Additional hexane (50 mL) was added and the precipitated amine salt was removed by filtration through Celite®. The filtrate was concentrated with the final traces of solvent were removed at high vacuum (0.15 Torr) to give the dial as a yellow semi-solid (0.63 g, *ca*. 95% pure by ^{1}H NMR using a quantitative internal standard; >90% yield).

^{1}H NMR (500 MHz, C_6D_6) δ: 9.46 (2H, s, HC= O × 2), 3.11 (4H, br s, H_2CO × 2), 2.82 (2H, ap dd, *J* = 13, 13 Hz, HC-7, HC-9), 2.42-239 (4H, m, HC-6, HC-7, HC-9, HC-10).

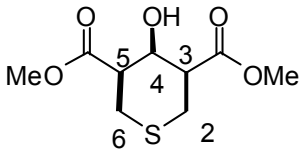
^{13}C NMR (125 MHz, C_6D_6) δ: 199.0 (× 2, C= O), 110.2 (C-5), 66.5 (CH_2O), 66.3 (CH_2O), 60.3 (× 2, C-6, C-10), 26.6 (× 2, C-7, C-9).

LRMS (EI), *m/z* (relative intensity): 216 ($[M]^+$, 12), 188 (9), 160 (6), 113 (11), 99 (100), 86 (5), 54 (18).

HRMS *m/z* calcd for $C_9H_{12}O_4S$ 216.0456, found 216.0458.

Anal. Calcd for $C_9H_{12}O_4S$: C, 49.99; H, 5.59. Found: C, 49.79; H, 5.59.

(3*R*,4*s*,5*S*)-Dimethyl tetrahydro-4-hydroxy-2H-thiopyran-3,5-dicarboxylate.



197ss

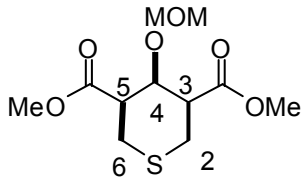
To a stirred solution of the keto diester **193** (1.49 g, 6.43 mmol) and citric acid (1.4 g, 7.28 mmol) in a mixture of EtOH (28 mL) and CH_2Cl_2 (28 mL) at -78 ^oC was added $NaCNBH_3$ (0.62 g, 9.92 mmol). The reaction mixture was allowed to slowly warm up to rt over 5 h, concentrated. The residue was dissolved in water (30 mL) and the solution extracted with EtOAc (50 mL x 3). The combined organic layers were dried (Na_2SO_4), concentrated and fractionated by FCC (50% EtOAc in hexanes) to afford the titled compound as a white solid (411 mg, 27%) and **197ss**, **197as**, and **197aa** (797 mg, 53%).

IR (DRIFT) ν_{max}: 3512, 2951, 1729, 1437, 1347, 1258, 1192, 1120 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.80 (1H, br s, HC-4), 3.76 (6H, br s, OCH_3 x 2), 3.16 (2H, dd, *J* = 12.5, 13.5 Hz, HC-2,6), 2.99 (1H, d, *J* = 2.5 Hz, OH), 2.77 (2H, ddd, *J* = 2, 3, 12.5 Hz, HC-3, 5), 2.60 (2H, dd, *J* = 3, 13.5 Hz, HC-2, 6)
LRMS (EI), *m/z* (relative intensity): 234 ($[M]^+$, 96), 184 (87), 174 (71), 155 (45), 125 (28), 115 (36), 97 (81), 54 (100).

HRMS *m/z* calcd. for $C_9H_{14}O_5S$: 234.0562; found: 234.0565.

Dimethyl (3R,4s,5S)-tetrahydro-4-(methoxymethoxy)-2H-thiopyran-3,5-dicarboxylate



198

DIPEA (1.93 mL, 10.94 mmol) was added to a stirred solution of **197ss** (411 mg, 1.75 mmol) and *n*-Bu_4NI (640 mg, 1.73 mmol) in CH_2Cl_2 (3 mL) at room temperature under argon. After 2 min, MOMCl (0.69mL, 9.05 mmol) was added and reaction mixture stirred vigorously for 24 h at the same temperature. The reaction mixture was poured into a separatory funnel containing 10% HCl (15 mL) and extracted with 20 mL CH_2Cl_2 (x 2). The combined organic layers were washed with $NaHCO_3$, dried (Na_2SO_4), concentrated, resuspended in 50% EtOAC:hex and then filtered through a silica pad to afford the titled compound (476 mg, 97%).

IR (DRIFT) ν_{max}: 2955, 1735, 1433, 1341, 1256, 1165, 1028, 937 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.82 (1H, dd, *J* = 2,2 Hz, HC-4), 4.55 (2H, br s, OCH_2O), 3.73 (6H, br s, OCH_3 x 2), 3.24 (3H, br s, OCH_3), 3.11 (2H, dd, *J* =

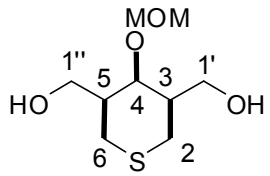
12.5, 12.5 Hz, HC-3, 5), 2.75 (2H, ddd, *J* = 2,3,12.5 Hz, HC-2ax, 6ax), 2.61 (2H, ddd, *J* = 2,3,12.5 Hz, HC-2eq, 6eq);

^{13}C NMR (125 MHz, $CDCl_3$) δ: 172. (s, C=O), 98.6 (t, OCH_2O), 76.2 (d, C-4), 56.6 (q, OCH_3), 52.2 (q, OCH_3 x 2), 49.8 (d, C-3, 5), 22.9 (t, C-2, 6);

LRMS (EI), *m/z* (relative intensity): 278 ($[M]^+$, 18), 247 (100), 228 (26), 201 (71), 185 (47), 157 (28), 130 (52), 97 (30);

HRMS *m/z* calcd. for $C_{11}H_{18}O_6S$: 278.0824; found: 278.0825.

(3R,4s,5S)-Tetrahydro-4-(methoxymethoxy)-2H-thiopyran-3,5-dimethanol



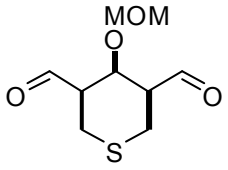
199

To a stirred suspension of $LiAlH_4$ (127 mg, 3.36 mmol) in THF (5 mL) at 0 ^oC was added dropwise a solution of **198** (467 mg, 1.68 mmol) in THF (3 mL). The mixture was removed from the ice bath and allowed to stir for 40 min at rt. The reaction was quenched by addition of 2N NaOH (1 mL) and then, filtered through a short column of celite® and Na_2SO_4. The combined filtrate and THF washings (100 mL) were concentrated to give a white solid that was homogeneous by ^{1}H NMR (354 mg, 95%).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.27 (2H, br s, OCH_2O), 4.21 (1H, br s, HC-4), 3.60-3.47 (4H, m, H_2C-1',H_2C-1''), 3.46 (3H, br s, OCH_3), 2.76 (2H, dd, *J* = 13, 13 Hz, HC-2, 6), 2.46 (2H, br s, OH x 2), 2.16 (2H, dd, *J* = 2, 13 Hz, HC-2, 6), 1.99 (2H, m, HC-3, 5);

^{13}C NMR (125 MHz, $CDCl_3$) δ: 99.0, 73.2, 63.5, 56.5, 45.9, 24.6.

(3R,4s,5S)-Tetrahydro-4-(methoxymethoxy)-2H-thiopyran-3,5-dicarbaldehyde.

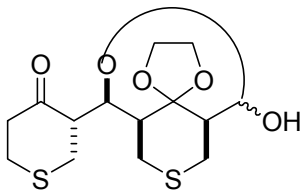


***meso* 200**

DMSO (0.117 mL, 1.64 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (0.072 mL, 0.83 mmol) in CH_2Cl_2 (3 mL) at -78 °C under argon. After 30 min, a solution of *cis meso* diol **199** (87 mg, 0.39 mmol) and Me_2S (0.107 mL, 1.45 mmol) in CH_2Cl_2 (1.4 mL) was added. After 30 min, *i*-Pr_2EtN (0.408 mL, 2.35 mmol) was added, and the reaction mixture was allowed to stir for another 2.5 h. The reaction mixture was then warmed to -10 °C over 10 min. Hexane (5 mL) and toluene (5 mL) was added and reaction mixture was concentrated to a volume of *ca.* 5 mL. Additional hexane (5 mL) was added and the precipitated amine salt was removed by filtration through Celite®. The filtrate was concentrated with the final traces of solvent were removed at high vacuum (0.15 Torr) to give the dial **200** (65 mg, ca. 95% pure by ^{1}H NMR using a quantitative internal standard; >90% yield).

^{1}H NMR (500 MHz, C_6D_6) δ: 9.55 (2H, br s, HCO x2), 4.88 (1H, br s, C-4), 4.49 (2H, br s, OCH_2O), 3.08 (3H, br s, OCH_3), 2.93 (2H, dd, *J* = 12.5, 13.5 Hz, HC-2), 2.64 (2H, dd, *J* = 2.5, 13.5 Hz, HC-2), 2.55 (2H, ddd, *J* = 1.5, 2.5, 12.5 Hz, HC-3).

(3*S*)-Tetahydro-3-[(1*R*,2*RS*,4*R*,5*S*)-2-hydroxyl-spiro[3-oxa-7-thiabicyclo[3.3.1]nonane-9,2'-[1,3]dioxolane]-4-yl]-4*H*thiopyran-4-one (201as).[170]



201as

Method 1

(*S*)-Proline (0.26 g, 2.1 mmol) and H_2O (0.33 mL, 18 mmol) was added to a stirred solution of thiopyranone **112** (2.15 g, 18.5 mmol) in dry DMSO (3.6 mL) at room temperature. After 1.5 h, a solution of the dial **223** (a 3.5:1 of dl and *meso* diastereomers, respectively; 1.0 g, 4.6 mmol) in DMSO (1 mL) was added. After 48 h, saturated aqueous NH_4Cl was added, and the mixture was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (70% ethyl acetate in hexane) to give the titled aldol adduct **201as** as a light yellow solid (1.05 g, 68%; a 3:1 mixture of lactol anomers with the 2'*S* isomer predominating).

IR (DRIFT) ν_{max}: 3204, 2917, 2851, 1715, 1434, 1320, 1105, 1027 cm^{-1};

^{1}H NMR (500 MHz, C_6D_6) δ: 5.39 (0.75H, dd, *J* = 1.5, 10.5 Hz, HC-4'), 5.25 (0.25H, dd, *J* = 2.5, 5.5 Hz, HC-2'), 5.11 (0.75H, d, *J* = 11 Hz, HC-2'), 4.91 (0.75H, d, *J* = 11 Hz, HO), 4.83 (0.25H, m, HC-4'), 3.36-3.05 (7.25H, m), 2.95 (0.25H, br d, *J* = 13 Hz), 2.85 (0.75H, ddd, *J* = 5, 12, 12 Hz, HC-5), 2.59 (0.75H, dd, *J* = 3.5, 14.5 Hz, HC-2), 2.50-2.00 (5.25H, m), 1.72 (0.25H, br s), 1.58 (0.75H, br s), 1.37 (0.75H, br s), 1.34 (0.25H, br s);

^{13}C NMR (500 MHz, C_6D_6) δ: 207.8, 206.9, 108.2, 107.9, 97.2, 96.0, 72.6, 69.9, 64.7, 64.6, 64.3, 64.0, 54.1, 53.7, 43.3, 42.9, 42.0, 41.6, 37.0, 36.7, 33.0, 32.8, 32.2, 32.1, 29.4, 26.2, 25.9, 24.6;

LRMS (EI), *m/z* (relative intensity): 332 ([M]$^+$, 7), 314 (6), 162 (8), 131 (5), 127 (7), 115 (27), 99 (100), 54 (17);

HRMS *m/z* calcd for $C_{14}H_{20}O_5S_2$ 332.0752, found 332.0757.

The absolute configuration for **201as** was determined by X-ray crystallographic analysis of the derived triol **226**. The ee of **201as** was determined by ^{1}H NMR of the derived *N*-trichloroacetylcarbamate (prepared in situ by addition of trichloroacetylisocyanate (TCI)) in the presence of (*R*)-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol (TFAE) as a chiral solvating agent. Both the NH and HC-2' protons for the enantiomers of the major diastereomer were sufficiently separated for measurement by integration.

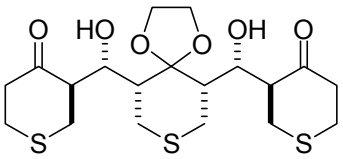
Method 2

To a stirred solution of freshly prepared lithium enolate **118** (M = Li) {prepared by adding MeLi (0.61 mL, 0.978 mmol) to a solution of enolsilane **117** (230 mg, 1.22 mmol) in ether (2 mL) at 0 ^{o}C and the mixture stirred at rt for 30 min prior to dilution with THF (4 mL)} in a mixture of THF and ether (2/1 v/v, 6 mL) at -78 ^{o}C was added the *meso* dialdehyde **196** (36 mg, 0.167 mmol) over 30 sec. The reaction was quenched within 5 min by adding sat NH_4Cl (5 mL) and was extracted with CH_2Cl_2 (10 mL x 2). The combined organic layers were dried over Na_2SO_4, concentrated and fractionated by FCC (70% ethyl acetate in hexane) to give the titled aldol adduct as a light yellow solid (32 mg, 58%)

Method 3

A solution of chlorodicyclohexylborane enolate **118** (M = $B(Chx)_2$) (19 mg, 0.163 mmol) in CH_2Cl_2 (1.5 mL) {prepared by adding chlorodicyclohexylborane (1.72 mmol) to a solution of ketone **112**(1.72 mmol) in CH_2Cl_2 (16 mL) followed by the addition of Et_3N (1.90 mmol) at 0 ^oC} was added to a stirred solution of the *meso* dialdehyde **196** (29 mg, 0.14 mmol) in CH_2Cl_2 (2 mL) at -78 ^oC. After 2 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 5 mL), MeOH (3 mL) and 30% aqueous H_2O_2 (1 mL). The mixture was vigorously stirred at 0 °C (ice-bath) for 10 min and then the excess peroxide was destroyed by addition of sat. aqueous Na_2SO_3 (5 mL). The reaction mixture was diluted with water and extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (70% ethyl acetate in hexane) to give the (±)-**201as** (18 mg, 40%).

(3*S*,3'*R*)-3,3'-((1*R*,1'*S*)-((6*R*,10*S*)-1,4-Dioxa-8-thiaspiro[4.5]decane-6,10-diyl)bis(hydroxymethylene))bis(dihydro-2H-thiopyran-4(3H)-one).



202as

Chlorodicyclohexylborane (1.52 mL, 1.47 g, 6.94 mmol) was added to a stirred solution of Et_3N (1.0 mL, 0.73 g, 7.2 mmol) in CH_2Cl_2 (80 mL) at 0 °C under Ar. After 2 min, a solution of thiopyranone (808 mg, 6.97 mmol) in CH_2Cl_2 (10 mL) was added dropwise via syringe. After 30 min, the mixture was cooled to –78 °C and, after 30 min, a solution of the meso dialdehyde (430 mg, 1.99 mmol) in CH_2Cl_2 (5 mL) was added dropwise via syringe. After 3.5 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 10 mL), followed by

MeOH (5 mL) and 30% aqueous H_2O_2 (3 mL). The mixture was vigorously stirred at 0 °C (ice-bath) for 10 min and then the excess peroxide was destroyed by addition of sat. aqueous Na_2SO_3 (10 mL). The reaction mixture was diluted with water and extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (60% ethyl acetate in hexane) to give the monoaldol **201as** (66 mg, 10%), the chiral bisaldol **202b** (71 mg, 8%) and the meso bisaldol **202as** (446 mg, 50%).

IR (DRIFT) ν_{max}: 3525, 2913, 1705, 1421, 1313, 1195, 1066, 916, 739 cm^{-1}.

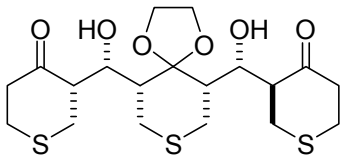
^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.40 (2H, ddd, *J* = 1.5, 3, 8.5 Hz, HC-1', HC-1"), 4.25 (4H, ap s, H_2CO x 2), 3.11 (2H, d, *J* = 3 Hz, HO x 2), 3.04 (2H, dd, *J* = 12, 14 Hz, HC-7, HC-9), 2.98-2.71 (12H, m), 2.57 (2H, ddd, *J* = 2, 2, 14 Hz, HC-7, HC-9), 1.94 (2H, ddd, *J* = 1.5, 2, 12 Hz, HC-6, HC-10).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 211.6 (s x 2, C-4', C-4"), 112.8 (s, C-5), 68.6 (d x 2, C1', C-1"), 67.6 (t, CH_2O), 66.2 (t, CH_2O), 56.3 (d x 2, C-3', C-3"), 51.6 (d x 2, C-6, C-10), 44.6 (t x 2, C-5', C-5"), 33.5 (t x 2, C-2', C-2"), 31.3 (t x 2, C-6', C-6"), 26.3 (t x 2, C-7, C-9).

LRMS (FAB), m/z (relative intensity): 449 ($[M+1]^+$, 100), 448 ($[M]^+$, 14), 349 (8), 315 (15), 287 (52), 225 (7), 161 (5), 132 (22), 99 (92).

HRMS *m/z* calcd. for $C_{19}H_{28}O_6S_3$: 448.1048 (449.1166 for M+H); found: 449.1124 (FAB).

(3*S*,3'*S*)-3,3'-((1*R*,1'*S*)-((6*R*,10*S*)-1,4-Dioxa-8-thiaspiro[4.5]decane-6,10-diyl)bis(hydroxymethylene))bis(dihydro-2H-thiopyran-4(3H)-one).

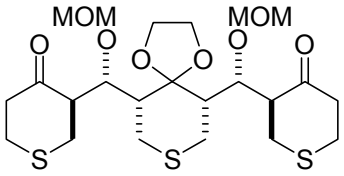


202b

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.65 (1H, ap d, *J* = 9 Hz, HC-1' or 1"), 4.34-4.28 (3H, m, HC-2 or 3 & 1" or 1'), 4.19 (2H, m, HC-3 or 2), 3.50 (2H, br s), 3.23 (1H, ap d, *J* = 3.5 Hz), 3.16 (1H, dd, *J* = 4, 13.5 Hz), 3.07-2.63 (19H, m), 2.53 (1H, ddd, *J* = 2.5, 2.5, 13.5 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 212.8, 210.1, 113.1, 68.4, 67.6, 66.7, 66.2, 56.64, 56.60, 51.0, 50.8, 45.1, 44.4, 33.5, 33.0, 31.5, 31.1, 26.3.

(3S,3'R)-3,3'-((1R,1'S)-((6R,10S)-1,4-Dioxa-8-thiaspiro[4.5]decane-6,10-diyl)bis((methoxymethoxy)methylene))bis(dihydro-2H-thiopyran-4(3H)-one).



205

DIPEA (2.5 mL, 1.9 g, 14 mmol) was added to a stirred solution of the meso aldol adduct **202as** (380 mg, 0.85 mmol) and *n*-Bu_4NI (942 mg, 2.55 mmol) in

CH_2Cl_2 (3 mL) at room temperature under argon. After 2 min, MOMCl (0.6 mL, 0.6 g, 8 mmol) was added and reaction mixture stirred vigorously for 3 days. The mixture was diluted with 10% aqueous HCl (15 mL) and extracted with CH_2Cl_2. The combined organic layers were washed with aqueous $NaHCO_3$, dried over Na_2SO_4, concentrated, resuspended in 50% EtOAc in hexanes and then filtered through a short silica pad. The filtrate was concentrated and fractionated by FCC (40% ethyl acetate in hexane) to afford the mono-MOM ether (208 mg, 50%) and bis-MOM ether (147 mg, 32%). Subjecting the recovered mono-MOM ether to the above conditions gave additional bis-MOM ether (124 mg, 27%).

IR (DRIFT) ν_{max}: 2902, 2827, 1711, 1426, 1319, 1276, 1152, 1040 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.79 (2H, d, *J* = 7 Hz, OCHO x 2), 4.50-4.46 (4H, m, OCHO x 2, H_2CO), 4.34-4.30 (4H, m, HC-1', HC-1", H_2CO), 3.30 (6H, br s, H_3CO x 2), 3.01-2.88 (10H, m, H_2C-2', H_2C-2", HC-5', HC-5",H_2C-6', H2C-6"), 2.81-2.77 (4H, m, HC-3', 3", HC-7, HC-9), 2.70-2.59 (4H, m, HC-5', HC-5", HC-7, HC-9), 2.09 (2H, m, *J* = 3, 3, 12 Hz, HC-6, 10).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 208.5 (s x 2, C-4', C-4"), 112.3 (s, C-5), 96.3 (t x 2, OCH_2O), 73.3 (d x 2, C-1', C-1"), 67.8 (t, CH_2O), 67.7 (t, CH_2O), 58.8 (d x 2, C-3' &3"), 56.7 (q x 2, CH_3O), 55.4 (d x 2, C-6, C-10), 43.5 (t x 2, C-5', C-5"), 33.4 (t x 2, C-2', C-2"), 31.0 (t x 2, C-6', C-6"), 28.3 (t x 2, C-7, C-9).

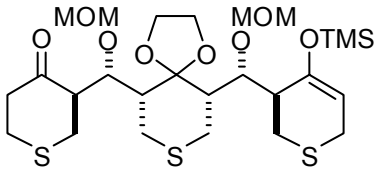
LRMS (EI), *m/z* (relative intensity): 536 ($[M]^+$, 1), 505 (2), 412 (2), 320 (14), 258 (19), 241 (10), 225 (35), 99 (100).

HRMS *m/z* calcd. for $C_{23}H_{36}O_8S_3$: 536.1572; found: 536.1578.

Alternative method

To a stirred solution of bis silyl enol ether **207**(45 mg, 0.07 mmol) in THF (5 mL) was added 10% aq HF (0.5 mL) and the mixture stirred at room temperature for 30 min. After complete hydrolysis (monitored by TLC), the mixture was poured into a separatory funnel containing $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (15 mL x 2). The combined organic layers were dried over Na_2SO_4, concentrated and filtered over a short silica pad with 60% EtOAc/Hexanes to afford the meso diketone **205** (32.6mg, 92%).

(3*R*)-3-((1*S*)-(Methoxymethoxy)((6*R*,10*S*)-10-((*R*)-(methoxymethoxy)((*R*)-4-(trimethylsilyloxy)-3,6-dihydro-2H-thiopyran-3-yl)methyl)-1,4-Dioxa-8-thiaspiro[4.5]decan-6-yl)methyl)dihydro-2H-thiopyran-4(3H)-one.



206

A solution of nBuLi in hexanes (2.6 M; 0.21 mL, 0.54 mmol) was added dropwise via syringe to a solution of (*R*,*R*)-bis(1-phenylethyl)amine (0.125 mL, 124 mg, 0.54 mmol) in THF (5.4 mL) at –78 °C under Ar. After stirring for 30 min. at –78 °C the resulting pink/purple solution was quickly transferred via cannula (ca. 15-30 sec.) into a well-stirred solution of diketone **205** (208 mg, 0.39 mmol) and TMSCl (0.48 mL, 0.41 mg, 3.9 mmol) in THF (14 mL) at –100 °C under Ar. After 15 min., the reaction was quenched by addition of acetone (0.5 mL) followed by Et_3N (0.5 mL) and sat. aqueous $NaHCO_3$. The resulting cold mixture was diluted with ethyl acetate and washed sequentially with 1% citric acid (x 4), sat. $NaHCO_3$ and brine, dried over Na_2SO_4, concentrated, and fractionated by FCC (10-20% ethyl acetate in hexane) to give the bis-silyl enol

ether (45 mg, 17%), recovered diketone (8 mg, 4%), and the titled mono-silyl (168 mg, 71%) ($[a]_D^{25}$ = +24; *c* 5.1, C_6H_6; >95% ee by ^1H NMR).

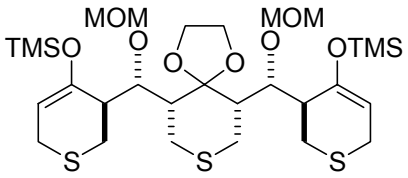
IR (DRIFT) ν_{max}: 2950, 2898, 1713, 1662, 1426, 1248, 1182, 1032 cm^{-1}.
^1H NMR (500 MHz, C_6D_6) δ: 4.96 (1H, dd, *J* = 4, 5 Hz, HC-5'), 4.74 (1H, d, *J* = 7 Hz, OCH_2O), 4.57 (1H, d, *J* = 6.5 Hz, OCH_2O), 4.48 (1H, d, *J* = 6.5 Hz, OCH_2O), 4.38 (1H, dd, *J* = 2.5, 8.5 Hz, HC-1''), 4.22-4.18 (1H, m, HC-2), 4.17 (1H, d, *J* = 7 Hz, OCH_2O), 4.15 (1H, dd, *J* = 2, 4.5 Hz, HC-1'), 4.05-3.97 (3H, m, HC-2, H_2C-3), 3.14 (3H, br s, H_3CO), 3.08 (1H, dd, *J* = 12, 14 Hz, HC-7), 3.01 (3H, br s, H_3CO), 2.90-2.83 (4H, m), 2.88 (1H, dd, *J* = 5, 16 Hz, HC-6'), 2.81 (1H, dd, *J* = 11, 14 Hz, HC-9), 2.75-2.60 (7H, m), 2.34-2.28 (3H, m, HC-5'', H_2C-6''), 2.16 (1H, ddd, *J* = 2.5, 4, 11 Hz, HC-10), 0.21 (9H, s, $(H_3C)_3Si$).

^{13}C NMR (125 MHz, C_6D_6) δ: 205.6 (s, C-4'), 152.3 (s, C-4'), 113.4 (s, C-5), 103.8 (d, C-5'), 96.7 (t, OCH_2O), 96.5 (t, OCH_2O), 75.5 (d, C-1'), 73.8 (d, C-1''), 67.9 (t, CH_2O), 67.4 (t, CH_2O), 59.1 (d, C-3''), 56.5 (q, CH_3O), 56.0 (q, OCH3), 55.9, 53.8 (d, C-6), 46.5 (d, C-3'), 43.5 (t, C-5''), 33.5 (t, C-2''), 31.1 (t, C-6''), 29.7 (t, C-7), 29.0 (t, C-9), 28.0 (t, C-2'), 25.7 (t, C-6'), 0.8 (q x 3, CH_3Si).

LRMS (EI), *m/z* (relative intensity): 608 ($[M]^+$, 1), 576 (10), 360 (67), 315 (8), 225 (26), 155 (26), 99 (100), 73 (35).

HRMS *m/z* calcd. for $C_{26}H_{44}O_8S_3Si$: 608.1968; found: 608.1955.

(6*R*,10*S*)-6-((*S*)-(Methoxymethoxy)((*R*)-4-(trimethylsilyloxy)-3,6-dihydro-2H-thiopyran-3-yl)methyl)-10-((*R*)-(methoxymethoxy)((*S*)-4-(trimethylsilyloxy)-3,6-dihydro-2H-thiopyran-3-yl)methyl)-1,4-Dioxa-8-thiaspiro[4.5]decane.



207

IR (DRIFT) ν_{max}: 2959, 2818, 1662, 1426, 1361, 1252, 1196, 1041 cm^{-1}.

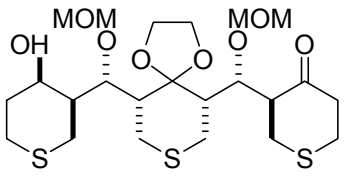
^{1}H NMR (500 MHz, C_6D_6) δ: 4.95 (2H, dd, *J* = 4, 4.5 Hz, HC-5', HC-5"), 4.61 (2H, d, *J* = 7 Hz, OCHO x 2), 4.51 (2H, d, *J* = 7 Hz, OCHO x 2), 4.12 (2H, dd, *J* = 2, 4.5 Hz, HC-1', HC-1"), 4.07 (4H, m, H_2CO x 2), 3.17 (6H, s, H_3CO x 2), 3.16 (2H, dd, *J* = 12, 13.5 Hz, HC-7, HC-9), 2.99 (2H, br d, *J* = 13.5 Hz, HC-7, HC-9), 2.96-2.83 (6H, m, HC-2', HC-2", H_2C-6', H_2C-6"), 2.67-2.59 (6H, m, HC-2', HC-2", HC-3', HC-3", HC-6, HC-10).

^{13}C NMR (125 MHz, C_6D_6) δ: 152.6 (s x 2, C-4', C-4"), 113.8 (d, C-5), 104.0 (d x 2, C-5', C-5"), 96.8 (t x 2, OCH_2O), 76.3 (d x 2, C-1', C-1"), 68.1 (t, CH_2O), 67.1 (t, CH_2O), 55.9 (q x 2, OCH_3 x 2), 54.8 (d x 2, C-6, C-10), 47.0 (d x 2, C-3', C-3"), 29.6 (t x 2, C-7, C-9), 28.6 (t x 2, C-2', C-2"), 25.7 (t x 2, C-6', C-6"), 0.7 (q x 6, CH_3Si).

LRMS (EI), *m/z* (relative intensity): 680 ($[M]^+$, 11), 648 (7), 359 (6), 280 (5), 215 (17), 115 (2), 99 (100), 73 (80).

HRMS *m/z* calcd. for $C_{29}H_{52}O_8S_3Si_2$: 680.2363; found: 680.2345.

(3S)-3-((1R)-((6S,10R)-10-((S)-((3S,4R)-4-Hydroxytetrahydro-2H-thiopyran-3-yl)(methoxymethoxy)methyl)-1,4-Dioxa-8-thiaspiro[4.5]decan-6-yl)(methoxymethoxy)methyl)dihydro-2H-thiopyran-4(3H)-one.



209

L-selectride (0.8 M solution in THF; 0.4 mL, 0.3 mmol) was added via syringe to a stirred solution of the mono TMS ether (54 mg, 0.635 mmol) in THF (5 mL) at -78 °C under argon. After 1 h, phosphate buffer (2 mL) and MeOH (3 mL) were added and the mixture stirred at 0 °C for 30 mins. 30% aqueous H_2O_2 (1 mL) was then added and the mixture was allowed to stir for 10 min at the same temperature. The excess peroxide was destroyed by addition of saturated Na_2SO_3 (5 mL). The mixture was diluted with brine (20 mL) and extracted with CH_2Cl_2 (× 3). The combined organic layers were dried over Na_2SO_4, concentrated and fractionated by FCC (EtOAc/hexanes 2/1) to give the titled compound {48 mg, 88%, $[\alpha]_D$ -57 (*c* 0.28, benzene)}.

IR (DRIFT) ν_{max}: 2928, 1710, 1424, 1269, 1186, 1148, 1034 cm^{-1}.

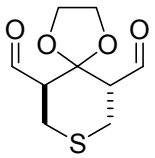
^{1}H NMR (500 MHz, C_6D_6) δ: 4.63 (1H, d, *J* = 7 Hz, OCH_2O), 4.42 (1H, d, *J* = 7 Hz, OCH_2O), 4.30 (1H, br s, HC-4'), 4.24 (1H, dd, *J* = 2.5, 7.5 Hz, C-1''), 4.14 (1H, d, *J* = 7 Hz, OCH_2O), 4.03 (1H, d, *J* = 7 Hz, OCH_2O), 4.02 (1H, ddd, *J* = 5.5, 8, 8 Hz, HC-2 or 3), 3.91 (1H, ddd, *J* = 8, 8, 8 Hz, HC-3 or 2), 3.78 (1H, ddd, *J* = 5.5, 8, 8 Hz, HC-2 or 3), 3.57-3.5 (2H, m, HC-3 or 2, 1'), 3.41-3.30 (3H, m), 3.00 (3H, br s, OCH_3), 2.95 (3H, br s, OCH_3), 2.84 (1H, dd, *J* = 4, 13.5 Hz, HC-9), 2.72-2.58 (7H, m), 2.43 (1H, ddd, *J* = 3, 8, 8HC-6 Hz), 2.39-2.27 (4H, m), 2.16-2.07 (3H, m, HC-5', 6' 3''), 1.92 (1H, dddd, *J* = 1.5, 3, 4.5, 11.5 Hz, HC-3'), 1.67 (1H, m, HC-6').

^{13}C NMR (125 MHz, C_6D_6) δ: 206.4, 113.3, 96.7, 96.4, 78.1, 73.6, 67.9, 67.7, 65.6, 59.1, 56.5, 56.3, 55.7, 55.2, 49.6, 43.8, 35.6, 33.4, 30.9, 29.6, 28.9, 26.2, 23.0.

LRMS (EI), *m/z* (relative intensity): 538 ([M]$^+$, 1), 322 (15), 289 (10), 260 (8), 227 (13), 131 (16), 99 (100), 54 (11).

HRMS *m/z* calcd. for $C_{23}H_{38}O_8S_3$: 538.1729; found: 538.1717.

(6*R*,10*R*)-*rel*-1,4-Dioxa-8-thiaspiro[4.5]decane-6,10-dicarboxaldehyde ((±)-**223)**.[170]



(±)-**223**

DMSO (6.80 mL, 95.3 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (4.16 mL, 47.7 mmol) in CH_2Cl_2 (80 mL) at -78 °C under argon. After 30 min, a solution of (±)-**18** (5.00 g, 22.7 mmol) and Me_2S (6.67 mL, 90.8 mmol) in CH_2Cl_2 (20 mL) was added. After 1.5 h, *i*-Pr_2EtN (23.7 mL, 136 mmol) was added, and the reaction mixture was allowed to warm to 0 °C over 20 min. The mixture was poured into a separatory funnel containing cold 10% aqueous HCl (100 mL). After thorough mixing, the organic layer was separated and the aqueous extracted with CH_2Cl_2 (× 3). The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, concentrated, and fractionated by FCC (60% ethyl acetate in hexane) to give a light yellow oil containing a 3.5:1
mixture of dl and *meso* diastereomers (by ^{1}H NMR), respectively (3.50 g, 71%).

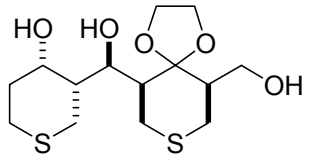
Method 2

Alternatively, a 1.5:1 mixture of the diesters (±)-**194a** and meso-**194c**, respectively (1.97 g, 7.13 mmol), in THF (20 mL) was added dropwise via syringe to a stirred suspension of $LiAlH_4$ (0.54 g, 14 mmol) in THF (100 mL) at 0 °C. The mixture was allowed to warm to room temperature and after 40 min, was quenched by addition of 2N NaOH (15 mL). The mixture was filtered through a short column with Celite® and Na_2SO_4 and washed with THF (500 mL). The combined filtrate and washings were concentrated to give a 1.5:1 mixture of (±)-**195** and *meso*-**195**, respectively, as a light yellow oil (1.29 g, 82%) that was homogeneous by ^1H NMR. Oxidation of this mixture as described above gave a 3.5:1 mixture of (±)-**223** and *meso*-**196** (by ^1H NMR), respectively (0.64 g, 50%).

^1H NMR (500 MHz, C_6D_6) δ: 9.62 (2H, br s, HC= O ×2), 3.12-3.02 (4H, m, H_2CO ×2), 2.73 (2H, dd, *J* = 7.5,14 Hz, HC-2, HC-6), 2.56 (2H, ddd, *J* = 1.5, 3.5, 14 Hz, HC-2, HC-6), 2.23 (2H, dd, *J* = 3.5, 7.5 Hz, HC-3, HC-5);

^{13}C NMR (125 MHz, C_6D_6) δ: 199.4 (× 2, C= O), 108.3, 65.1 (× 2, CH_2O), 55.1 (× 2, C-3. C-5), 27.1 (× 2, C- 2, C-6).

(3*R*,4*S*)-3-{(*R)*-Hydroxy-[(6*S*,10*R*)-10-hydroxymethyl-1,4-dioxa-8-thiaspiro[4.5]dec-6-yl]methyl}-tetrahydro-2*H*thiopyran-4-ol (226).[170]



226

L-selectride (0.8M solution in THF; 4 mL, 3 mmol) was added via syringe to a stirred solution of the lactol **201as** (212 mg, 0.635 mmol) in THF (10 mL) at -78 °C under argon. After 1 h, 2 N aqueous NaOH (2 mL) and 30% aqueous

H_2O_2 (1 mL) were added and the mixture was allowed to stir for 10 min at 0 °C. The resulting mixture was diluted with saturated Na_2SO_3 (5 mL) and brine (20 mL) and was extracted with CH_2Cl_2 (× 3) and the combined organic layers were dried over Na_2SO_4 and concentrated to give a light yellow residue. The residue was taken up in ethanol (5 mL) and excess $NaBH_4$ was added. After 1 h, 2N NaOH (2 mL) and brine (10 mL) were added and the mixture was extracted with CH_2Cl_2 (× 3). The combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (40% acetone in hexane) to give the titled compound as a white solid (150 mg, 70%): mp 163-165 °C (acetone/hexane); $[\alpha]_D$ +40 (*c* 1.0, MeOH).

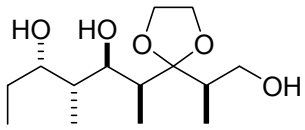
IR (DRIFT) ν_{max}: 3389, 3240, 2935, 1422, 1314, 1200, 1045, 877 cm^{-1};
^{1}H NMR (500 MHz, CD_3OD) δ: 4.29 (1H, ddd, *J* = 2, 2, 5 Hz, HC-4), 4.16-4.00 (3H, m, HC-2", HC-3"), 3.99 (1H, dd, *J* = 2.5, 8 Hz, HC-1'), 3.90 (1H, m, HC-3"), 3.85 (1H, dd, *J* = 3.5, 10.5 Hz, H_2COH), 3.31 (1H, m, *J* = 9.5, 10.5 Hz, H_2COH), 3.03 (1H, ddd, *J* = 2.5, 13.5, 13.5 Hz, HC-6), 2.99 (1H, dd, *J* = 11.5, 14 Hz, HC-7"), 2.85 (1H, dd, *J* = 11.5, 13.5 Hz, HC-2), 2.82 (1H, ddd, *J* = 2.5, 3.5, 13 Hz, HC-9"), 2.69 (1H, dd, *J* = 13, 13 Hz, HC-9"), 2.58 (1H, ddd, *J* = 2.5, 3, 14 Hz, HC-7"), 2.26 (1H, dddd, *J* = 1.5, 3.5, 5, 13.5 Hz, HC-6), 2.20-2.13 (2H, m, HC-2, HC-5), 2.04 (1H, dddd, *J* = 3.5, 3.5, 9.5, 13 Hz, HC-10"), 1.96 (1H, ddd, *J* = 2.5, 3, 11.5 Hz, HC-6"), 1.86-1.81 (2H, m, HC-3, HC-5);

^{13}C NMR (125 MHz, CD_3OD) δ: 112 (s, C-5"), 70.9 (d, C-1'), 68.0 (t, CH_2O), 67.6 (t, CH_2O), 66.6 (d, C-4), 61.9 (t, CH_2OH), 54.9 (d, C-10"), 52.2 (d, C-6"), 47.0 (d, C-3), 35.9 (t, C-5), 30.4 (t, C- 9"), 27.8 (t, C-7"), 26.4 (t, C-2), 23.4 (t, C-6);

LRMS (EI), *m/z* (relative intensity): 336 ($[M]^+$, 5), 163 (16), 162 (74), 129 (15), 100 (100), 99 (48), 55 (12);

HRMS *m/z* calcd for $C_{14}H_{24}O_5S_2$ 336.1065, found 336.1050.

(*R*)-2-[(1*S*,2*R*,3*R*,4*S*)-2,4-Dihydroxy-1,3-dimethylhexyl]-β-methyl-1,3-dioxolane-2-ethanol (227).[170]



227

A suspension of freshly prepared Raney Ni (W-2) (1 mL settled volume) in ethanol (1 mL) was added to a well stirred solution of the triol **226** (60 mg, 0.18 mmol) in methanol (3 mL) and THF (3 mL) and the resultant mixture was heated under reflux. After 40 min (reaction complete by TLC), the supernatant was filtered through a pad of Celite® and the residue was suspended in methanol (10 mL) and after stirring for several minutes, the supernatant was filtered. This process was repeated as required. The combined filtrates were concentrated and the residue taken up in CH_2Cl_2 and the solution was dried over Na_2SO_4, concentrated, and fractionated by PTLC (80% ethyl acetate in hexane) to give the titled compound (27 mg, 55%; this procedure has not been optimized and the modest yield is results from difficulty in quantitatively isolating the very polar product): $[\alpha]_D$ -3 (*c* 0.8, $CHCl_3$).

IR (**D**RIFT) ν_{max}: 3417, 2970, 2846, 1463, 1366, 1200, 1103, 1060 cm^{-1};

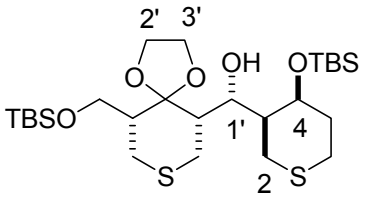
^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.15-4.03 (4H, m, H_2CO × 2), 3.93 (1H, dd, *J* = 1, 10 Hz, HC-2'), 3.71-3.66 (2H, m, HC-α, HC-4'), 3.57 (1H, dd, *J* = 4, 11 Hz, HC-α), 2.74 (2H, br s, HO × 2), 2.31-2.27 (1H, m, HC-β), 2.21 (1H, dq, *J* = 1, 7 Hz, HC-1'), 1.83 (1H, ddq, *J* = 2.5, 10, 7 Hz, HC-3'), 1.58-1.42 (2H, m, H_2C-5'), 1.02 (3H, d, *J* = 7 Hz, H_3CC-β), 1.01 (3H, t, *J* = 7 Hz, H_3C-6), 0.95 (3H, d, *J* = 7 Hz, H_3CC-1'), 0.76 (3H, d, *J* = 7 Hz, H_3CC-3');

^{13}C NMR (125 MHz, $CDCl_3$) δ: 117.5 (s, C-2), 75.6 (d, C-4'), 73.0 (d, C-2'), 67.2 (t, CH_2O), 66.4 (t, CH_2O), 64.7 (t, C-α), 41.5 (d, C-β), 40.2 (d, C-1'(3')), 40.1 (d, C-3'(1')), 26.0 (t, C-5'), 12.9 (q, CH_3C-β or C-6), 11.9 (q, CH_3C-3'), 11.4 (q, CH_3C-β or C-6), 6.8 (q, CH_3C-1');

LRMS (CI, NH_3), *m/z* (relative intensity): 294 ($[M+18]^+$, 1), 277 ($[M+1]^+$, 1), 215 (100), 197 (17), 191 (16), 161 (8), 131 (36), 101 (7);

HRMS *m/z* calcd for $C_{12}H_{23}O_5$ (MC_2H_5) 247.1545, found 247.1554 (EI).

(*R*)-((6*S*,10*R*)-10-((Tert-butyldimethylsilyloxy)methyl)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)((3*S*,4*S*)-4-(tert-butyldimethylsilyloxy)tetrahydro-2H-thiopyran-3-yl)methanol.



228

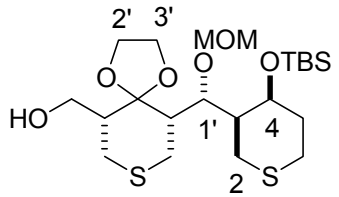
TBSOTf (0.29 mL, 1.26 mmol) and Et_3N (0.5 mL, 6.81 mmol) were added sequentially to a suspension of triol **226** (139 mg, 0.413 mmol) in CH_2Cl_2 (4 mL). After 20 mins, the clear solution was poured into a separatory funnel containing $NaHCO_3$ (15 mL) and was extracted with CH_2Cl_2 (15 mL x 2). The the combined organic layers were dried (Na_2SO_4), concentrated and the residue was filtered through a short silica pad to afford the titled compound (230 mg, 98%).

^{1}H NMR (500 MHz, C_6D_6) δ: 4.45 (1H, dd, *J* = 1, 4.5 Hz), 3.96 (1H, dd, *J* = 1, 10 Hz), 3.80-3.73 (2H, m), 3.50 (1H, m), 3.43 (1H, m), 3.34 (1H, m), 3.27 (1H, m), 3.11-3.04 (2H, m), 2.97 (1H, ddd, *J* = 3, 3, 13.5 Hz), 2.87-2.80 (2H, m), 2.71 (1H,

br s), 2.51 (1H, ddd, *J* = 2.5, 2.5, 13.5 Hz), 2.25 (1H, m), 2.04-1.98 (3H, m), 1.90 (1H, m), 1.81 (1H, m), 1.66 (1H, m), 0.99 (9H, br s), 0.94 (9H, brs), 0.13 (3H, br s), 0.04 (3H, br s), 0.03 (3H, br s), 0.02 (3H, br s);

^{13}C NMR (125 MHz, C_6D_6) δ: 113.2, 68.8, 67.2, 66.3, 65.7, 62.4, 54.5, 49.5, 46.7, 35.9, 30.0, 26.5, 26.4, 26.3, 24.4, 22.5, 18.80, 18.77, -3.8, -4.5, -4.9, -5.0.

((6*R*,10*S*)-10-((*R*)-((3*S*,4*S*)-4-(Tert-butyldimethylsiloxy)tetrahydro-2*H*-thiopyran-3-yl)(methoxymethoxy)methyl)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)methanol.



230

DIPEA (1 mL, 6.85 mmol) was added to a stirred solution of **228** (393 mg, 0.69 mmol) and *n*-Bu_4NI (765 mg, 2.07 mmol) in CH_2Cl_2 (2 mL) at room temperature under argon. After 2 min, a solution of MOMCl (0.22 mL, 2.74 mmol) was added and reaction mixture stirred vigorously for 4 days at the same temperature. The reaction mixture was poured into a separatory funnel containing 10% HCl (15 mL) and extracted with 20 mL CH_2Cl_2 (x 2). The combined organic layers were washed with $NaHCO_3$, dried (Na_2SO_4), concentrated, resuspended in 50% EtOAC:hex and then filtered through a silica pad to afford **229** (382 mg, 90%) that was homogeneous by TLC and used without any further purification.

To a stirred solution of **229** (161 mg, 0.264 mmol) in THF (10 mL) at 0 ^oC (ice bath) was added 10% aq HF (9 mL). After 2 h, the reaction was quenched by the addition of sat Na_2CO_3 (30 mL) and the mixture was extracted with CH_2Cl_2.

the combined organic layers were dried (Na_2SO_4), concentrated and the residue was filter through a short silica pad to afford the title compound (106 mg, 81%) and **229** (6 mg, 4%).

IR (DRIFT) ν_{max}: 3439, 2932, 1467, 1421, 1256, 1187, 1039, 977 cm^{-1};

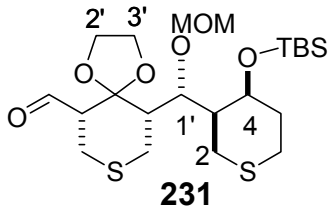
^{1}H NMR (500 MHz, C_6D_6) δ: 4.48 (2H, br s, OCH_2O), 4.37 (1H, dd, *J* = 1, 4.5 Hz, HC-1'), 3.70-3.60 (2H, m, HC-2' or 3'), 3.55 (1H, dd, *J* = 3, 8.5 Hz, HC-11'), 3.51-3.45 (2H, m, HC-4, 3' or 2'), 3.37 (1H, m, HC-3' or 2'), 3.18 (1H, dd, *J* = 11.5, 12 Hz), 3.17 (3H, br s, OCH_3), 3.13 (1H, dd, *J* = 3, 13.5 Hz), 3.07 (1H, dd, *J* = 7.5, 10.5 Hz), 2.99 (1H, dd, *J* = 12, 12 Hz), 2.74 (1H, dd, *J* = 12, 13.5 Hz), 2.68 (1H, ddd, *J* = 3, 3, 13.5 Hz), 2.60 (1H, ddd, *J* = 3, 3, 13.5 Hz), 2.38 (1H, m), 2.34 (1H, ddd, *J* = 3, 3, 12 Hz), 2.07-2.01 (2H, m), 1.98-1.90 (2H, m), 0.97 (9H, br s, $(CH_3)_3$), 0.11 (3H, br s, $SiCH_3$), 0.01 (3H, br s, $SiCH_3$);

^{13}C NMR (125 MHz, C_6D_6) δ: 112.7, 97.7, 76.4, 67.0, 66.9, 66.8, 62.8, 56.4, 54.2, 52.8, 50.5, 36.4, 29.9, 29.0, 26.7, 25.4, 22.6, 18.9, -2.8, -4.5;

LRMS (EI), *m/z* (relative intensity): 494 ($[M]^+$, 1), 437 (46), 375 (12), 300 (13), 202 (100), 161 (32), 115 (46), 99 (79);

HRMS *m/z* calcd. for $C_{22}H_{42}O_6S_2Si$: 494.2192; found: 494.2199.

((6*R*,10*S*)-10-((*R*)-((3*S*,4*S*)-4-(Tert-butyldimethylsilyloxy)tetrahydro-2H-thiopyran-3-yl)(methoxymethoxy)methyl)-1,4-dioxa-8-thiaspiro[4.5]decane-6-carbaldehyde.



231

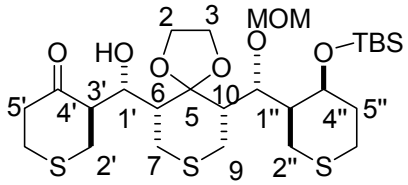
DMSO (49 µL, 0.69 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (30 µL, 0.83 mmol) in CH_2Cl_2 (6 mL) at -78 °C under argon. After 40 min, a solution of alcohol **230** (63 mg, 0.13 mmol) and Me_2S (0.10 mL, 1.4 mmol) in CH_2Cl_2 (1 mL) was added. After 3 h, i-Pr_2EtN (0.19 mL, 1.3 mmol) was added, and the reaction mixture was allowed to warm to room temperature over 20 min. Hexane (5 mL) and toluene (5 mL) were added and reaction mixture was concentrated to a volume of *ca*. 5 mL. Additional hexane (5 mL) was added and the precipitated amine salt was removed by filtration through Celite®. The filtrate was concentrated and the final traces of solvent were removed at high vacuum (0.15 Torr) to give the titled aldehyde (70 mg, ca. 95% pure by ^{1}H NMR using a quantitative internal standard; >80% yield).

^{1}H NMR (500 MHz, C_6D_6) δ: 9.56 (1H, br s, HCO), 4.42 (2H, ap q, *J* = 6 Hz, OCH_2O), 4.34 (1H, m), 3.56-3.51 (2H, m), 3.43 (1H, ddd, *J* = 4, 8, 8 Hz), 3.28 (1H, ddd, *J* = 4, 8, 8 Hz), 3.20-3.11 (2H, m), 3.14 (3H, br s, OCH_3), 3.02 (1H, dd, *J* = 11.5, 13 Hz), 2.93 (1H, dd, *J* = 12, 14 Hz), 2.57-2.48 (3H, m), 2.34 (1H, ap d, *J* = 12.5 Hz), 2.27 (1H, ddd, *J* = 2.5, 2.5, 12 Hz), 2.02 (1H, ap d, *J* = 12.5 Hz), 1.94-1.90 (2H, m), 1.65 (1H, m), 1.21 (1H, ap d, *J* = 6 Hz), 0.96 (9H, br s, $(CH_3)_3$), 0.09 (3H, br s, CH_3), 0.03 (3H, br s, CH_3).

LRMS (EI), *m/z* (relative intensity): 492 ([M]$^+$, 1), 435 (24), 299 (4), 203 (22), 127 (18), 99 (100), 89 (13), 73 (15).

HRMS *m/z* calcd. for $C_{22}H_{40}O_6S_2Si$: 492.2036; found: 492.1982.

(3*R*)-3-((1*S*)-((6*R*,10*S*)-10-((*R*)-((3*S*,4*S*)-4-(Tert-butyldimethylsilyloxy)tetrahydro-2H-thiopyran-3-yl)(methoxymethoxy)methyl)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)(methoxymethoxy)methyl)dihydro-2H-thiopyran-4(3H)-one.



233

IR (DRIFT) ν_{max}: 3525, 2936, 1710, 1431, 1258, 1205, 1050, 842 cm^{-1}.

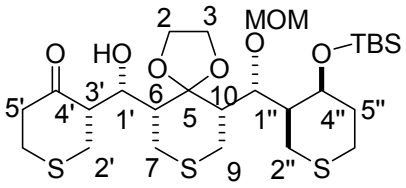
^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.64 (1H, ap d, *J* = 5.5 Hz, OCH_2O), 4.58 (1H, ap d, *J* = 5.5 Hz, OCH_2O), 4.39 (1H, ap d, *J* = 3.5 Hz, HC-1'), 4.31-4.09 (5H, m, HC-2, 3, 4''), 3.51 (1H, dd, *J* = 2, 10.5 Hz, HC-1''), 3.40 (3H, br s, OCH_3), 3.13-3.08 (2H, m), 3.03-2.68 (10H, m), 2.62 (1H, ddd, *J* = 2.5, 2.5, 14 Hz), 2.52 (1H, ddd, *J* = 2.5, 2.5, 14 Hz), 2.24-2.16 (4H, m), 1.90 (1H, ap d, *J* = 12 Hz), 1.84-1.78 (2H, m), 1.58 (9H, br s, $C(CH_3)$), 0.12 (3H, br s, $Si(CH_3)$), 0.09 (3H, br s, $Si(CH_3)$).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 212.4, 112.5, 97.4, 75.6, 68.6, 67.5, 66.5, 65.9, 56.6, 56.6, 53.3, 51.5, 49.9, 44.9, 35.7, 33.4, 31.2, 28.5, 26.4, 26.3, 24.6, 22.1, 18.6, -2.9, -4.8.

LRMS (EI), *m/z* (relative intensity): 631[M + 23]$^+$

HRMS *m/z* calcd. for $C_{27}H_{48}O_7S_3Si$: 608.2331 (M + Na = 631.2224); found: 631.2216(M + Na).

(3*S*)-3-((1*S*)-((6*R*,10*S*)-10-((*R*)-((3*S*,4*S*)-4-(Tert-butyldimethylsilyloxy)tetrahydro-2H-thiopyran-3-yl)(methoxymethoxy)methyl)-1,4-dioxa-8-thiaspiso[4.5]decan-6-yl)(methoxymethoxy)methyl)dihydro-2H-thiopyran-4(3H)-one.



234

A solution of $TiCl_4$ (18 µL, 0.16 mmol) in CH_2Cl_2 (0.5 mL) was added to the solution of thiopyranone **112** (19 mg, 0.16 mmol) in CH_2Cl_2 (2.5 mL) at -78 ^oC under argon to give a fine orange slurry. After 15 min, DIEA (23 µL, 0.18 mmol) was added giving a deep red solution that was allowed to stir for 1 h. A solution of aldehyde **231** (15 mg, 0.03 mmol) in CH_2Cl_2 (1 mL) was added to the mixture and the reaction stirred for another 1 h. The mixture was poured into phosphate buffer pH 7 (5 mL) at 0 ^oC and the organic phase was separated. The aqueous phase was extracted twice with 10 mL CH_2Cl_2. and the combined organic layers were dried (Na_2SO_4), concentrated, and fractionated by FCC (EtOAc:hex, 1:2) to afford **233** (9.2 mg, 50%, $[\alpha]^{24}_D$ +36 (*c* = 0.16, MeOH)) and **234** (8.4 mg, 45%, $[\alpha]^{24}_D$ -30 (*c* = 0.1, MeOH)).

IR (DRIFT) ν_{max}: 3525, 2936, 1710, 1425, 1261, 1199, 1056, 842 cm^{-1}.

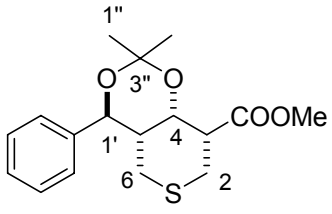
^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.65-4.62 (2H, m, HC-1' & H_2CO), 4.59 (1H, ap d, *J* = 6 Hz, H_2CO), 4.35 (1H, ap d, *J* = 4.5 Hz, C-4''), 4.23-4.21 (4H, m, C-2 & 3), 3.56 (1H, dd, *J* = 2, 9 Hz, HC-1'), 3.40 (3H, br s, OCH_3), 3.14-2.80 (10H, m), 2.69-2.80 (5H, m), 2.24-2.15 (4H, m), 1.86-1.78 (3H, m), 0.94 (9H, br s, $(CH_3)_3$), 0.15 (3H, br s, CH_3), 0.09 (3H, br s, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 210.1, 113.5, 97.0, 75.7, 67.6, 66.8, 66.2, 65.9, 57.0, 56.6, 53.1, 51.5, 49.8, 44.3, 35.8, 32.8, 31.4, 28.4, 26.3, 24.6, 22.1, 18.5, -2.8, -4.8.

LRMS (EI), *m/z* (relative intensity): 631[M + 23]$^+$

HRMS *m/z* calcd. for $C_{27}H_{48}O_7S_3Si$: 608.2331 (M + Na = 631.2224); found: 631.2243(M + Na).

Methyl (4S,4aS,8R,8aS)-hexahydro-2,2-dimethyl-4-phenylthiopyrano[4,3-d][1,3]dioxine-8-carboxylate.



236

To a stirred solution of the diol **163ass** (13 mg, 0.05 mmol) in an mixture of CH_2Cl_2 (2 mL) and 2,2-dimethoxy propane (1 mL) was added a catalytic amount of p-TsOH (ca 1 mg). After the disappearance of the diol (*ca.* 25 mins), the reaction was diluted with CH_2Cl_2 (10 mL), washed sequentially with $NaHCO_3$ (5

mL) and water (2 mL). The organic phase was dried, concentrated and fractionated by PTLC (25% EtOAc in hexanes) to afford the title compound (11 mg, 75% yield).

IR (DRIFT) ν_{max}: 2988, 1731, 1373, 1265, 1223, 1163, 1062 cm^{-1}.

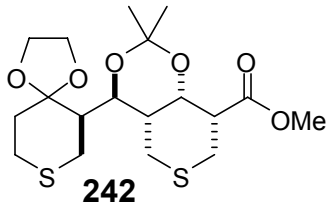
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.33 (5H, m, Ph), 4.69 (1H, dd, *J* = 3,3 Hz, HC-4), 4.33 (1H, d, *J* = 6 Hz, HC-4'), 3.73 (3H, br s, OCH_3), 2.93-3.03 (2H, m, HC-2ax, 6ax), 2.85 (1H, ddd, *J* = 3,3,12 Hz, HC-3), 2.64 (1H, ddd, *J* = 2,5,13 Hz, HC-2eq), 2.43 (1H, ddd, *J* = 2,5,13 Hz, HC-6eq), 2.17 (1H, dddd, *J* = 3,5,6,13 Hz, HC-5), 1.43 (3H, br s, OCH_3), 1.36 (3H, br s, OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.23, 141.66, 128.71, 127.94, 126.04, 101.90, 64.20, 51.78, 46.74, 46.04, 27.70, 25.21, 23.76, 23.60.

LRMS (EI), *m/z* (relative intensity): 322 ($[M]^+$, 15), 264 (22), 233 (12), 187 (11), 158 (73), 117 (33), 98 (100).

HRMS *m/z* calcd. for $C_{17}H_{22}O_4S$: 322.1239; found: 322.1236.

Methyl (4*S*,4a*R*,8*R*,8a*S*)-2,2-dimethyl-4-((S)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)hexahydrothiopyrano[4,3-d][1,3]dioxine-8-carboxylate



242

To a stirred solution of the aldol **168as** (13 mg, 0.036 mmol) under argon at -40 °C in a mixture of MeCN (1 mL) and AcOH (1 mL) was added $NaBH(OAc)_3$ (38 mg, 0.179 mmol) in one portion. The reaction was warmed up to -10 °C and

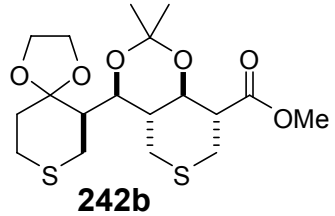
allowed to stir at that temperature for 5 h. Sat. sodium potassium tatrate (4mL) was added, the reaction was removed from the cooled bath and stirred at rt for 30 min. The mixture was diluted with EtOAc (10 mL) and washed with $NaHCO_3$ (5 mL x 2). The organic phase was dried, concentrated and fractionated by PTLC (EtOAc/hexanes, 4/1) to afford a 14:1 ratio of **241** (10 mg, 77%).

To a stirred solution of a 5:1 ratio of diol **241** (71 mg, 0.194 mmol) in a mixture of CH_2Cl_2 (3 mL) and 2,2-dimethoxy propane (1 mL) was added a catalytic amount of *p*-TsOH (13mg, 0.068 mmol). After the disappearance of the diol (1 h), the reaction was diluted with CH_2Cl_2 (10 mL), washed in succession with $NaHCO_3$ (5 mL) and water (2 mL). The organic phase was dried, concentrated and fractionated by PTLC (25% EtOAc in Hexanes) to afford the title compound (20 mg, 26% yield) and **242b** (4 mg, 5%).

^{1}H NMR (500 MHz, C_6D_6) δ: 4.30 (1H, ap br s, HC-4), 3.70 (1H, dd, *J* = 5.5, 5.5 Hz, HC-1'), 3.52 (4H, ap br s, H_2C-2'' & H_2C-3''), 3.41 (3H, br s, OCH_3), 2.99-2.90 (2H, m), 2.71-2.43 (6H, m), 2.26 (1H, dd, *J* = 3, 13.5 Hz), 1.91 (1H, m), 1.83-1.73 (2H, m), 1.54 (1H, ddd, *J* = 3.5, 9.5, 13.5 Hz), 1.18 (3H, br s, CH_3), 1.16 (br s, CH_3).

^{13}C NMR (125 MHz, C_6D_6) δ: 172.7, 109.2, 101.7, 71.5, 65.2, 65.1, 64.7, 51.9, 50.7, 47.6, 44.3, 36.9, 28.5, 28.3, 27.4, 26.1, 24.5, 23.8.

(4*S*,4a*R*,8*R*,8a*R*)-Methyl 2,2-dimethyl-4-((*S*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)hexahydrothiopyrano[4,3-d][1,3]dioxine-8-carboxylate.

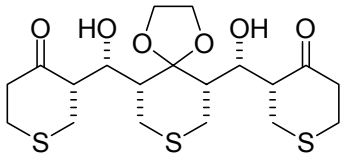


242b

^{1}H NMR (500 MHz, C_6D_6) δ: 3.76 (1H, dd, *J* = 10.5, 10.5 Hz, HC-4), 3.64-3.53 (4H, m, H_2C-2" &H_2C-3"), 3.43 (3H, br s, OCH_3), 3.37 (1H, dd, *J* = 4.5, 10.5 Hz, HC-1'), 3.09 (1H, dd, *J* = 12.5, 13.5 Hz), 2.83-2.62 (6H, m), 2.32 (1H, ap d, *J* = 12.5 Hz), 2.22 (1H, ap d, *J* = 13.5 Hz), 2.03 (1H, dd, *J* = 12.5, 13 Hz), 1.96 (1H, ddd, *J* = 1, 2.5, 12 Hz), 1.80 (1H, ddd, *J* = 3, 13, 13 Hz), 1.60 (1H, ddd, *J* = 4, 13, 13 Hz), 1.31 (3H, br s, CH_3), 1.23 (3H, br s, CH_3).

^{13}C NMR (125 MHz, C_6D_6) δ: 170.9, 109.6, 98.7, 74.5, 69.6, 65.3, 65.2, 51.8, 48.1, 45.0, 38.9, 37.6, 31.2, 30.6, 29.2, 27.5, 27.2, 19.6.

(3*R*,3'*S*)-3,3'-((1*R*,1'*S*)-((6*R*,10*S*)-1,4-Dioxa-8-thiaspiro[4.5]decane-6,10-diyl)bis(hydroxymethylene))bis(dihydro-2H-thiopyran-4(3H)-one).



244

DMAP (32 mg, 0.26 mmol) was added to a solution of **202b** (35 mg, 0.61 mmol) in acid free $CHCl_3$ (0.66 mL) (the acid was removed by passing the solvent through basic Al_2O_3). After 48 h, the reaction mixture was washed with 10% citric acid (10 mL), the organic layer dried over Na_2SO_4, concentrated and fractionated on PTLC (60% EtOAc in hexanes) to afford the titled compound (11.5 mg, 33%), **202b** (14 mg, 40%), and **202as** (3.5 mg, 10%).

Alternative method

A similar ratio of products were obtained when **202as**.was subjected to the same reaction.

IR (DRIFT) ν_{max}: 3508, 2922, 1696, 1420, 1313, 1199, 1056, 733 cm^{-1}.

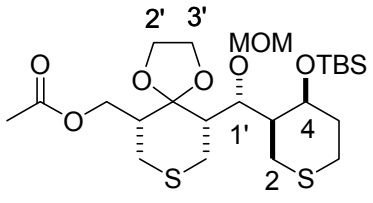
^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.62 (2H, ddd, *J* = 2.5, 2.5, 7.5 Hz, HC-1 & 1"), 3.64 (2H, ap t, *J* = 6.5 Hz, HC-2 or 3), 3.42 (2H, ap t, *J* = 6.5 Hz, HC-3 or 2), 2.95 (2H, dd, *J* = 11.5, 14 Hz), 2.89 (2H, dd, *J* = 8, 14 Hz), 2.78 (2H, dd, *J* = 4, 13.5 Hz), 2.66 (2H, m), 2.62 (2H, ddd, *J* = 4, 7.5, 7.5 Hz), 2.28-2.22 (8H, m), 2.18-2.11 (2H, m), 1.95 (2H, ddd, *J* = 2.5, 2.5, 11.5 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 209.3, 114.0, 67.5, 66.7, 66.4, 57.6, 51.6, 44.4, 32.5, 31.0, 27.0.

LRMS (CI, NH_3), m/z (relative intensity): 466 ($[M + 18]^+$, 1), 332 (36), 315 (100), 284 (11), 234 (91), 217 (61), 201 (17), 99 (61).

HRMS *m/z* calcd. for $C_{19}H_{28}O_6S_3$: 448.1048 (For M + NH_4, 466.1386) ; found: 466.2679(M + NH_4).

((6*R*,10*S*)-10-((*R*)-((3*S*,4*S*)-4-(Tert-butyldimethylsilyloxy)tetrahydro-2H-thiopyran-3-yl)(methoxymethoxy)methyl)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)methyl acetate.



245

A mixture of **230** (10 mg, 0.02 mmol), pyridine (0.5 mL), and acetic anhydride (0.25 mL) was stirred at room temperature for 12 h. The mixture was diluted with CH_2Cl_2 (10 mL) and washed sequentially with 10% HCl (5 mL) and $NaHCO_3$ (5

mL), dried over Na_2SO_4, and concentrated to afford the titled compound as an oil (10.5 mg, 96%).

IR (DRIFT) ν_{max}: 2926, 1741, 1467, 1364, 1227, 1039, 828, 71 cm^{-1};

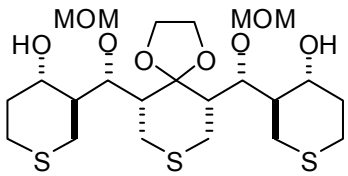
^{1}H NMR (500 MHz, C_6D_6) δ: 4.47 (2H, br s, OCH_2O), 4.35 (1H, d, *J* = 4.5 Hz), 4.25 (1H, dd, *J* = 4.5, 10.5 Hz, HC-1''), 3.70 (1H, dd, *J* = 9.5, 10.5 Hz), 3.65 (1H, ap q, HC-2' or 3'), 3.61-3.57 (1H, m, HC-3' or 2'), 3.54 (1H, dd, *J* = 3, 8 Hz, C-1'), 3.48-3.44 (1H, m, HC-2' or 3'), 3.31 (1H, ap q, HC-2' or 3'), 3.19-3.11 (2H, m), 3.16 (3H, br s, OCH_3), 3.01 (1H, dd, *J* = 12, 14 Hz), 2.78 (1H, dd, *J* = 12, 13.5 Hz), 2.69-2.64 (2H, m), 2.67-2.30 (3H, m), 2.02 (1H, dddd, *J* = 2, 4, 4, 13.5 Hz), 1.96 (1H, ddd, *J* = 1.5, 2.5, 8.5 Hz), 1.93 (1H, m), 1.66 (1H, m), 1.63 (3H, br s, CH_3), 1.32 (2H, m), 0.96 (9H, br s, $C(CH_3)_3$);

^{13}C NMR (125 MHz, C_6D_6) δ: 170.5, 111.7, 97.7, 76.5, 67.2, 66.8, 63.9, 56.4, 52.7, 51.4, 50.5, 36.4, 30.5, 30.1, 29.0, 26.7, 26.5, 25.3, 22.5, 20.7, 18.9, -2.8, -4.5;

LRMS (CI, NH_3), m/z (relative intensity): 537 ($[M+1]^+$, 25), 505 (100), 479 (60), 203 (26), 171 (12), 144 (17), 113 (66), 99 (35);

HRMS *m/z* calcd. for $C_{24}H_{44}O_7S_2Si$: 53.2370; found: 537.3035 (M+H).

(3*S*,4*S*,4'*R*,5'*R*)-3,5'-((1*S*,1'*S*)-((6*R*,10*S*)-1,4-Dioxa-8-thiaspiro[4.5]decane-6,10-diyl)bis((methoxy methoxy)methylene))bis(tetrahydro-2*H*-thiopyran-4-ol).



259maa

To a stirred solution of *meso* diketone **205** (55 mg, 0.102 mmol) in a mixture of EtOH (2 mL) and THF (1 mL) at 0 ^{o}C was added in one portion excess $NaBH_4$ After 1 h at the same temperature, the reaction mixture was quenched by adding 2 M aq NaOH (2 mL) and then was diluted with brine (5 mL) and extracted with CH_2Cl_2 (10 mL x 3). The combined organic layers were were dried (Na_2SO_4), concentrated and fractionated by FCC using (EtOAc) to afford the titled compound (22 mg, 39%) and a 1.5:1 mixture of **260as** and **260mss** respectively (28 mg, 50%).

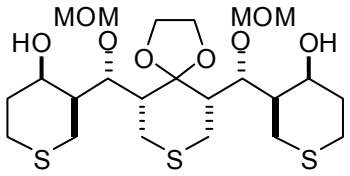
IR (DRIFT) ν_{max}: 3455, 2910, 1420, 1261, 1147, 1090, 1033, 906 cm^{-1}.

^{1}H NMR (500 MHz, C_6D_6) δ: 4.49 (2H, d, *J* = 7 Hz, OCH_2O), 4.31 (2H, d, *J* = 7 Hz, OCH_2O), 4.08 (2H, dd, *J* = 2, 4 Hz, HC-1' & 1''), 4.00 (2H, m, HC-2 or 3), 3.79 (2H, m, HC-3 or 2), 3.30 (2H, ddd, *J* = 4, 10, 10 Hz, HC-4' & 4''), 3.10 (6H, br s, OCH_3 x 2), 2.92 (2H, dd, *J* = 12, 12 Hz, HC-7, 9), 2.78 (2H, ddd, *J* = 2.5, 2.5, 13.5 Hz, HC-2' & 2''), 2.72 (2H, br s, OH x 2), 2.64 (2H, ddd, *J* = 2.5, 2.5, 13.5 Hz, HC 7, 9), 2.40-2.20 (8H, m, HC-6, 10, 6' 6', 6'', 6'', 2', 2''), 2.14 (2H, m, HC-3', 3''), 2.00 (2H, m, HC-5' & 5''), 1.73 (2H, dddd, *J* = 4, 11, 12, 13 Hz, HC-5' & 5'').

^{13}C NMR (125 MHz, C_6D_6) δ: 114.6, 95.6, 72.7, 70.8, 67.7, 67.6, 56.0, 53.6, 52.5, 37.5, 29.9, 28.3, 28.2.
LRMS (EI), *m/z* (relative intensity): 540 ($[M]^+$, 1), 322 (47), 289 (39), 229 (34), 173 (15), 132 (11), 99 (100), 89 (14).

HRMS *m/z* calcd. for $C_{23}H_{40}O_8S_3$: 540.1885; found: 540.1913.

(3*S*,4*R*,4'*S*,5'*R*)-3,5'-((1*S*,1'*R*)-((6*R*,10*S*)-1,4-Dioxa-8-thiaspiro[4.5]decane-6,10-diyl)bis((methoxymethoxy)methylene))bis(tetrahydro-2*H*-thiopyran-4-ol).



259mss

L-selectride (0.8 M solution in THF; 0.54 mL, 0.43 mmol) was added via syringe to a stirred solution of the *meso* diketone **205** (23 mg, 0.04 mmol) in THF (5 mL) at -78 °C under argon. After 2 h, 2 M NaOH (2 mL) and 30% aqueous H_2O_2 (1mL) was added and the mixture was allowed to stir for 10 min at 0 ^oC. The excess peroxide was destroyed by addition of saturated Na_2SO_3 (5 mL), and the mixture was diluted with brine (10 mL) and extracted with CH_2Cl_2 (5 mL × 3). The combined organic layers were dried over Na_2SO_4, concentrated and fractionated by FCC (EtOAc/hexanes 4/1) to give the titled compound (21 mg, 91%).

IR (DRIFT) ν_{max}: 3481, 2898, 2821, 1420, 1350, 1090, 932 cm^{-1}.

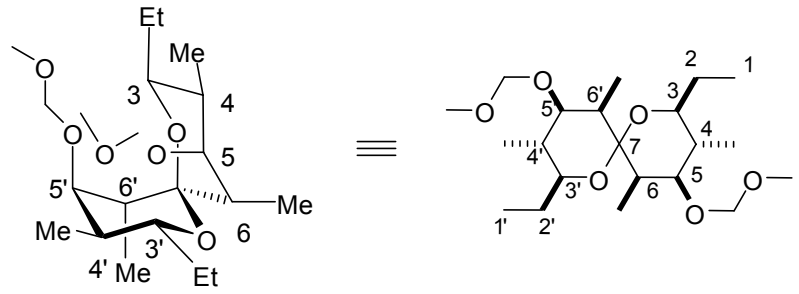
^{1}H NMR (500 MHz, C_6D_6) δ: 4.69 (2H, d, *J* = 6.5 Hz, OCH_2O), 4.55 (2H, d, *J* = 6.5 Hz, OCH_2O), 4.32-4.22 (6H, m, HC-2, 3, 4', 4''), 3.65 (2H, dd, *J* = 3.5, 5 Hz, HC-1' & 1''), 3.45 (2H, brs, OH x 2), 3.42 (6H, brs, OCH_3), 3.11 (4H, brs), 2.64 (4H, m), 2.34-2.20 (8H, m), 1.87 (4H, m).

^{13}C NMR (125 MHz, C_6D_6) δ: 113.3, 96.5, 77.4, 67.9, 67.8, 65.1, 56.7, 54.4, 48.7, 34.8, 28.9, 25.6, 22.6.

LRMS (EI), *m/z* (relative intensity): 540 ([M]$^+$, 5), 322 (30), 289 (28), 260 (15), 229 (23), 173 (22), 99 (100).

HRMS *m/z* calcd. for $C_{23}H_{40}O_8S_3$: 540.1885; found: 540.1872.

(2*R*,3*S*,5*S*,8*S*,9*R*,10*R*)-2,8-Diethyl-4,10-bis(methoxymethoxy)-3,5,9,11-tetramethyl-1,7-dioxaspiro[5.5]undecane.



preferred conformer of **262maa** **262maa**

To a stirred solution of *meso* diol **260maa** (34 mg, 0.063 mmol) in CH_2Cl_2 (1 mL) at ambient temperature was added sequentially Et_3N (70 µL, 0.504 mmol), TMSCl (32 µL, 0.252 mmol) and DMAP (4 mg, 0.032 mmol). After 1 h, the reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with $NaHCO_3$, the organic phase dried over Na_2SO_4, and concentrated. The residue was filtered through a short silica pad (hexanes/acetone, 3:1 v/v) and the filtrate concentrated to give an oil that was homogenous by TLC. A suspension of freshly prepared Raney Ni (W-2) (2 mL settled volume) in ethanol (2 mL) was added to a well stirred solution of the crude residue in ethanol (4 mL) and the resultant mixture was heated under reflux. After 12 h (reaction complete by TLC), the supernatant was diluted with methanol/ acetone (1:1 v/v, 150 mL) and the mixture heated at 40 ^oC for 30 mins. The hot mixture was filtered through a pad

of Celite® and the combined filtrates were concentrated and the residue taken up in CH_2Cl_2 and the solution was dried over Na_2SO_4, concentrated, and fractionated by PTLC (80% hexane in ethyl acetate) to give the titled compound (11 mg, 49%).

IR (DRIFT) ν_{max}: 2964, 2934, 1456, 1379, 1145, 1092, 1044, 1002 cm^{-1}.

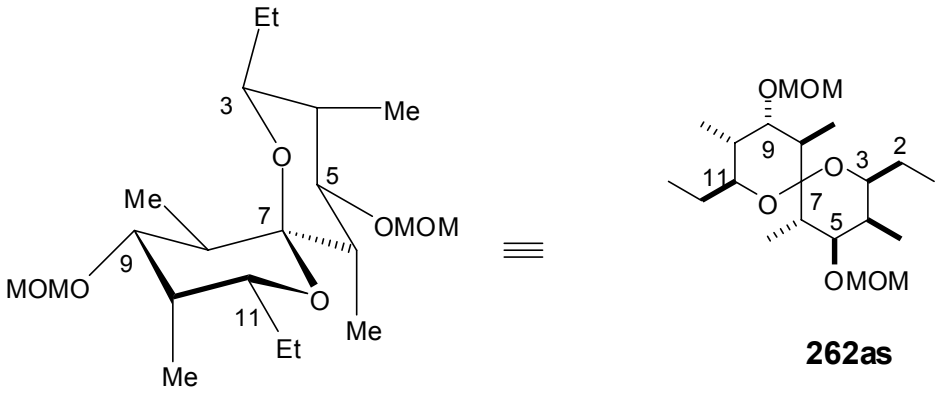
^{1}H NMR (500 MHz, C_6D_6) δ: 4.70 (1H, d, *J* = 7 Hz, OCH_2O), 4.56 (1H, d, *J* = 7 Hz, OCH_2O), 4.49 (1H, d, *J* = 7 Hz, OCH_2O), 4.32 (1H, d, *J* = 7 Hz, OCH_2O), 4.25 (1H, ddd, *J* = 3, 7.5, 10.5 Hz, HC-3'), 3.59-3.54 (3H, m, HC, 5, 5', 3), 3.67 (3H, br s, OCH_3), 3.32 (3H, br s, OCH_3), 2.84 (1H, dq, *J* = 3, 7 Hz, HC-6), 2.21 (1H, dq, *J* = 3.5, 7 Hz, HC-6'), 1.81-1.64 (4H, m, HC-4, 4', 2, 2'), 1.50 (1H, ddq, *J* = 7.5, 7.5, 15 Hz, HC-2), 1.40 (1H, ddq, *J* = 7.5, 7.5, 16 Hz, HC-2'), 1.15-1.09 (9H, m, HC-1, 1', 9'), 0.96 (3H, d, *J* = 7 Hz, HC-9), 0.89 (3H, d, *J* = 7 Hz, HC-8), 0.86 (3H, d, *J* = 7 Hz, HC-8').

^{13}C NMR (125 MHz, C_6D_6) δ: 100.0, 96.3, 96.1, 82.6, 81.6, 74.0, 71.5, 56.1, 55.9, 37.2, 34.0, 33.9, 33.1, 27.2, 26.8, 16.4, 14.3, 13.6, 10.2, 9.5.

LRMS (EI), *m/z* (relative intensity): 388 ($[M]^+$, 3), 261 (100), 217 (46), 199 (10), 166 (14), 155 (20), 102 (15), 83 (69).

HRMS *m/z* calcd. for $C_{21}H_{40}O_6$: 388.2825; found: 388.2836.

(2*S*,3*S*,4*S*,6*S*,11*S*)-2,8-Diethyl-4,10-bis(mehtoxymethoxy)-3,5,9,11-tetramethyl-1,7-dioxaspiro[5.5]undecane.



Preferred conformer of **262as**

262as

To a stirred solution of a 1.5 :1 mixture of diols **260as** and **260mss** (21 mg, 0.039 mmol) in CH_2Cl_2 (1 mL) at ambient temperature was added sequentially Et_3N (44 µL, 0.339 mmol), TMSCl (20 µL, 0.158 mmol) and DMAP (2.5 mg, 0.02 mmol). After 1 h, the reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with $NaHCO_3$, the organic phase dried over Na_2SO_4, and concentrated. The residue was filtered through a short silica pad (hexanes/acetone, 3:1 v/v) and the filtrate concentrated to give homogenous oil by TLC. A suspension of freshly prepared Raney Ni (W-2) (4 mL settled volume) in ethanol (2 mL) was added to a well stirred solution of the crude residue in ethanol (4 mL) and the resultant mixture was heated under reflux. After 24 h (reaction complete by TLC), the supernatant was diluted with methanol/ acetone (1:1 v/v, 150 mL) and the mixture heated at 40 ^oC for 30 mins. The hot mixture was filtered through a pad of Celite® and the combined filtrates were concentrated and the residue taken up in CH_2Cl_2 and the solution was dried over Na_2SO_4, concentrated, and fractionated by PTLC (80% hexane in ethyl acetate) to give the titled compound (4.3 mg, 47%) and **262mss** (2.2 mg, 36%).

IR (DRIFT) ν_{max}: 2952, 2892, 1462, 1379, 1145, 1104, 1038, 984 cm^{-1}.

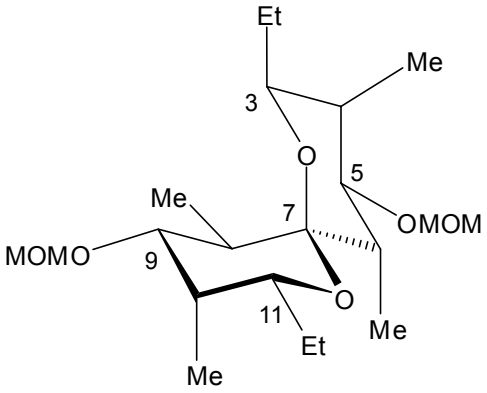
^{1}H NMR (500 MHz, C_6D_6) δ: 4.64 (1H, d, *J* = 6.5 Hz, OCH_2O), 4.53 (1H, d, *J* = 6.5 Hz, OCH_2O), 4.52 (1H, d, *J* = 6.5 Hz, OCH_2O), 4.47 (1H, d, *J* = 6.5 Hz, OCH_2O), 3.90 (1H, dd, *J* = 7, 11 Hz, HC-5 or 5'), 3.87 (1H, dd, *J* = 4.5, 11 Hz, HC-5' or 5), 3.72 (1H, ddd, *J* = 2, 4, 9 Hz, HC-3'), 3.48 (1H, ddd, *J* = 3, 8.5, 8.5 Hz, HC-3), 3.23 (3H, br s, OCH_3), 3.20 (3H, br s, OCH_3), 2.30 (1H, dq, *J* = 7, 11 Hz, HC-6), 2.15 (1H, dq, *J* = 6.5, 11 Hz, HC-6), 2.00-1.92 (2H, m, HC-4 or 4'), 1.64 (1H, ddq, *J* = 7.5, 9,14.5 Hz, HC-2'), 1.56-1.41 (2H, m, HC-2), 1.30 (3H, d, *J* = 6.5 Hz, CH_3), 1.24 (1H, ddq, *J* = 4, 7.5, 14.5 Hz, HC-2'), 1.18 (3H, d, *J* = 7.5 Hz, CH_3), 1.05 (3H, d, *J* = 7 Hz, CH_3), 1.01 (3H, t, *J* = 7.5 Hz, CH_3), 0.99 (3H, t, *J* = 7.5 Hz, CH_3), 0.83 (3H, d, *J* = 7 Hz, CH_3).

^{13}C NMR (125 MHz, C_6D_6) δ: 103.0, 96.0, 95.8, 80.2, 75.9, 74.5, 72.0, 55.8, 55.7, 41.0, 37.5, 36.7, 36.4, 28.5, 26.5, 13.2, 13.0, 12.1, 11.8, 11.7, 6.0.

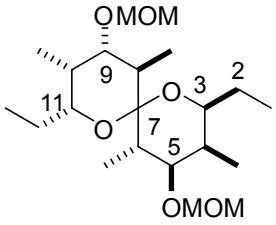
LRMS (EI), *m/z* (relative intensity): 388 ($[M]^+$, 1), 261 (100), 228 (22), 217 (27),166 (34), 155 (17), 83 (28), 69 (25).

HRMS *m/z* calcd. for $C_{21}H_{40}O_6$: 388.2825; found: 388.2840.

(2*S*,3*S*,4*S*,6*S*,11*S*)-2-8-Diethyl-4,10-bis(meethoxymethoxy)-3,5,9,11-tetramethyl-1,7-dioxaspiro[5.5]undecane.



Preferred conformer of **262mss**



262mss

To a stirred solution of *meso* diol **260mss** (10 mg, 0.019 mmol) in CH_2Cl_2 (1 mL) at ambient temperature was added sequentially Et_3N (20 µL, 0.148 mmol), TMSCl (10 µL, 0.074 mmol) and DMAP (*ca* 1 mg). After 1 h, the reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with $NaHCO_3$, the organic phase dried over Na_2SO_4, and concentrated. The residue was filtered through a short silica pad (hexanes/acetone, 3:1 v/v) and the filtrate concentrated to give an oil that was homogenous by TLC. A suspension of freshly prepared Raney Ni (W-2) (3 mL settled volume) in ethanol (2 mL) was added to a well stirred solution of the crude residue in ethanol (4 mL) and the resultant mixture was heated under reflux. After 24 h (reaction complete by TLC), the supernatant was diluted with methanol/ acetone (1:1 v/v, 100 mL) and the mixture heated at 40 ^{o}C for 30 mins. The hot mixture was filtered through a pad of Celite® and the combined filtrates were concentrated and the residue taken up in CH_2Cl_2 and the solution was dried over Na_2SO_4, concentrated, and fractionated by PTLC (80% hexane in ethyl acetate) to give the titled compound (3.5 mg, 49%).

IR (DRIFT) ν_{max}: 2964, 2886, 1462, 1145, 1104, 1038, 978 cm^{-1}.

^{1}H NMR (500 MHz, C_6D_6) δ: 4.69 (1H, d, *J* = 7 Hz, OCH_2O), 4.62 (1H, d, *J* = 7 Hz, OCH_2O), 4.55 (1H, d, *J* = 7 Hz, OCH_2O), 4.47 (1H, d, *J* = 7 Hz, OCH_2O), 4.13 (1H, ddd, *J* = 2, 5.5, 8 Hz, HC-3), 4.02 (1H, dd, *J* = 5, 11 Hz, HC-5), 4.77 (1H, dd, *J* = 4.5, 12 Hz, HC-5',) 3.65 (1H, ddd, *J* = 2, 3.5, 9 Hz, HC-3'), 3.25 (3H, br s, OCH_3), 3.20 (3H, br s, OCH_3), 2.41 (1H, dq, *J* = 7,12 Hz, HC-6'), 2.31 (1H, dq, *J* = 7,11 Hz, HC-6), 2.00 (1H, ddq, *J* = 2,4.5,7 Hz, HC-4), 1.86 (1H, ddq, *J* = 2,4.5,7 Hz, HC-4'), 1.66-1.55 (2H, m, HC-2 & 2'), 1.29 (1H, ddq, *J* = 5.5, 7.5, 8 Hz, HC-2), 1.26 (3H, d, *J* = 7 Hz, HC-9'), 1.16 (3H, d, *J* = 7 Hz, HC-9), 1.14 (1H, ddq, *J* = 3.5,7.5,9 Hz, HC-2'), 1.06 (3H, d, *J* = 7 Hz, HC-8'), 1.03 (3H, d, *J* = 7 Hz, HC-8), 0.96 (3H, t, *J* = 7.5 Hz, HC-1'), 0.92 (3H, t, *J* = 7.5 Hz, HC-1).

^{13}C NMR (125 MHz, C_6D_6) δ: 102.3, 95.8, 95.3, 80.3, 80.1, 77.9, 72.5, 55.8, 55.7, 42.4, 37.8, 36.2, 35.7, 27.5, 26.2, 14.8, 13.3, 11.4, 11.0, 5.9, 5.8.

LRMS (EI), *m/z* (relative intensity): 388 ($[M]^+$, 1), 261 (100), 199 (48), 169 (27), 155 (67) ,102 (27), 83 (32).

HRMS *m/z* calcd for $C_{21}H_{40}O_6$: 388.2825; found: 388.2827.

Chapter 5

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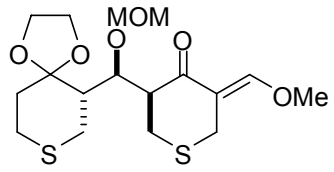
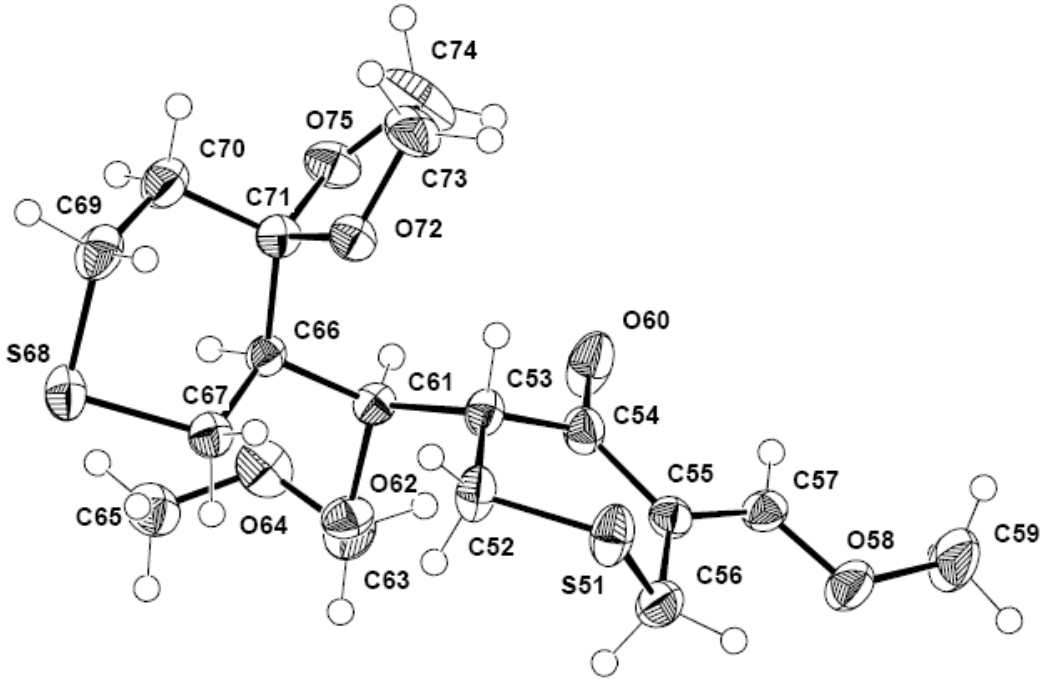
Appendices.

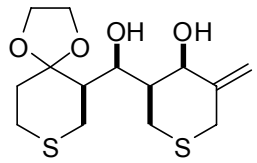
Appendix A : ORTEP diagram of 190sa



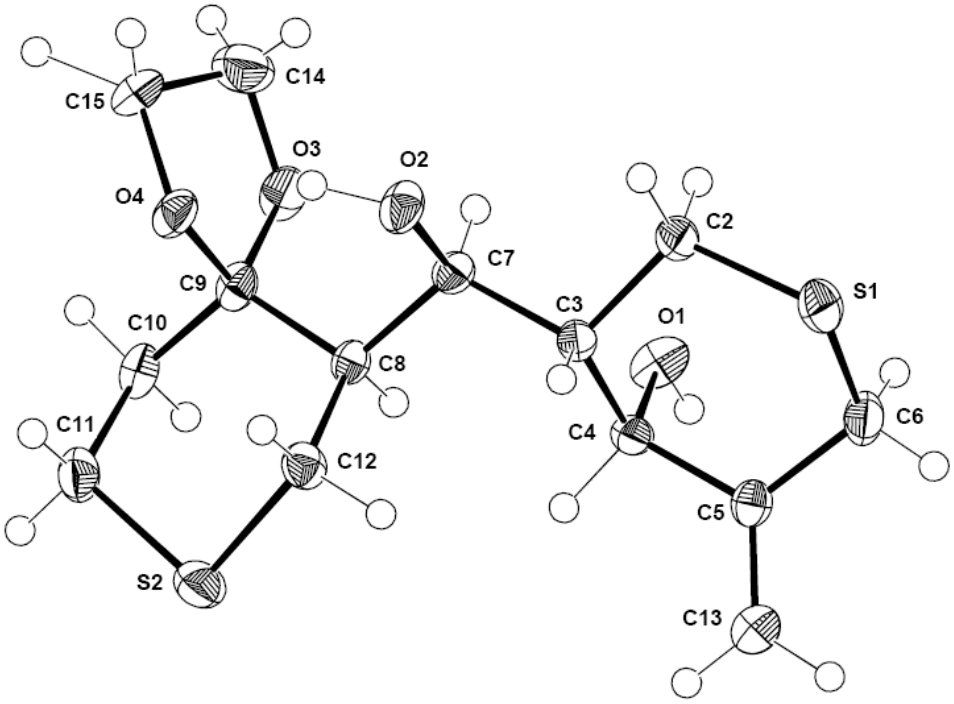
190sa



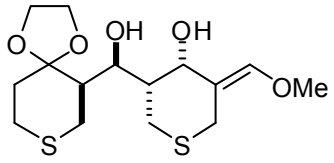
Appendix B: ORTEP diagram of 182

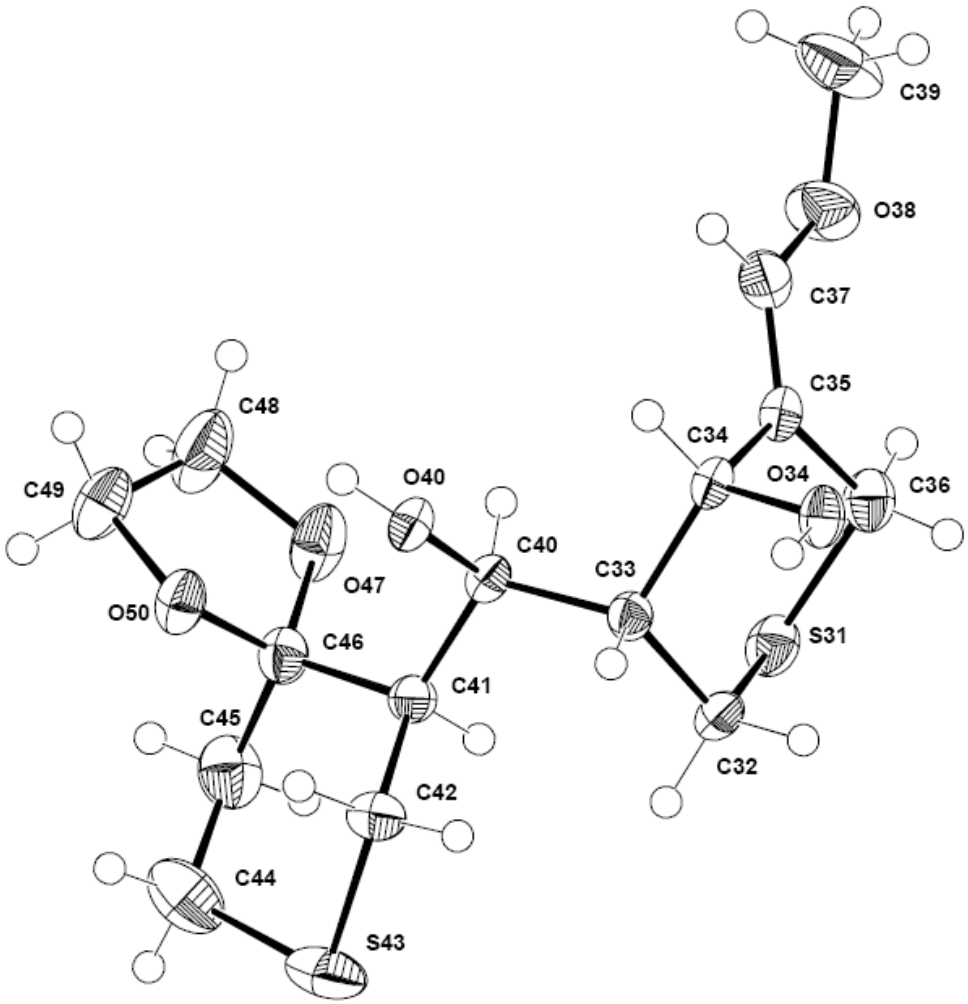


182

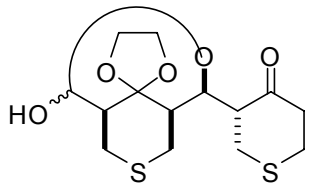


Appendix C: ORTEP diagram of 181aas

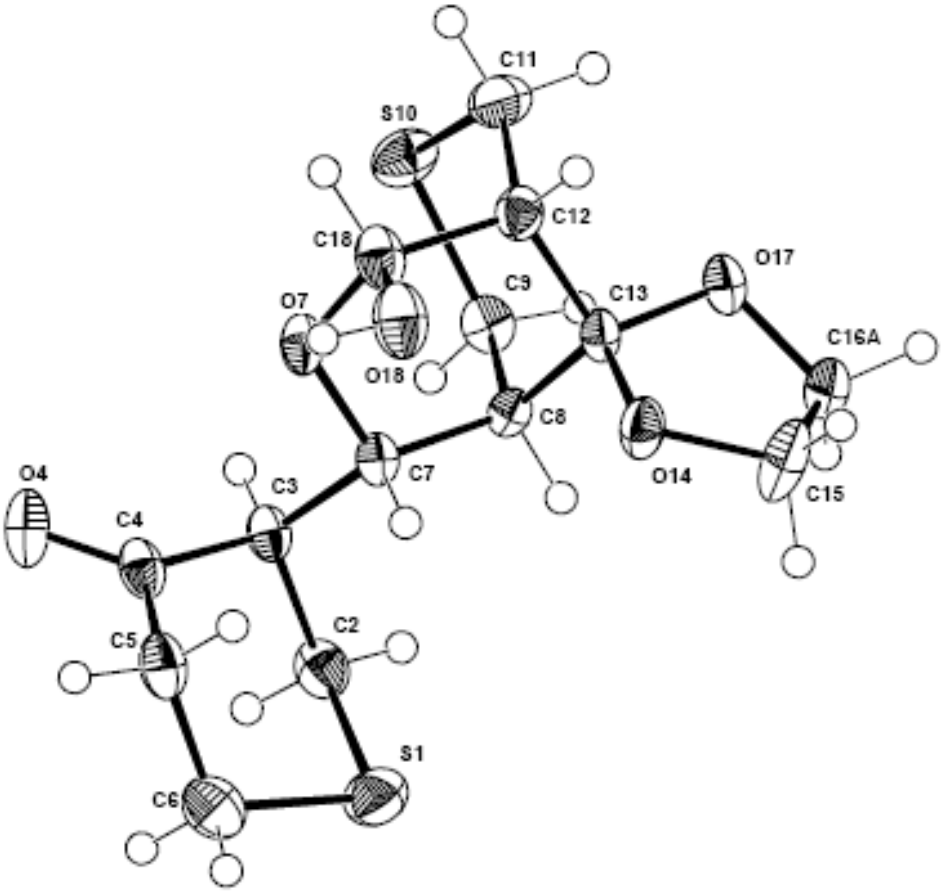




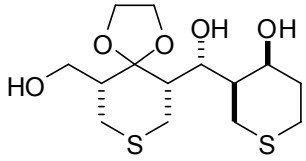
Appendix D: ORTEP diagram of 201ass



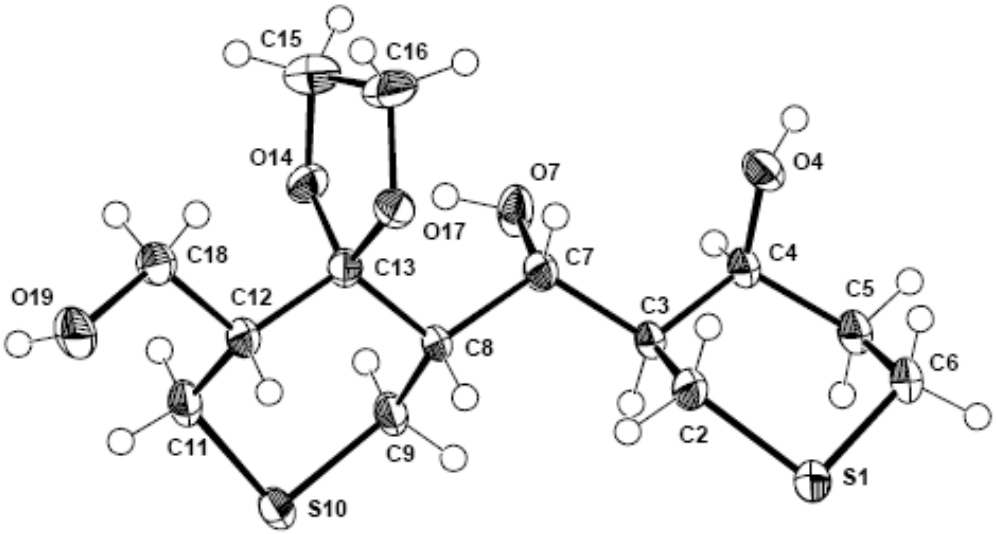
201ass



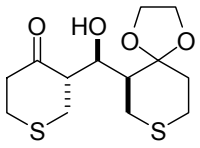
Appendix E: ORTEP diagram of 226



226

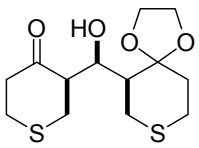


Appendix F: ^{13}C NMR chemical shift difference of 202as with 120a-d



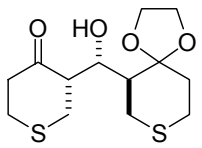
as

120a



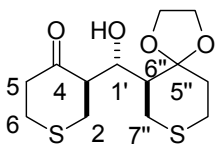
ss

120b



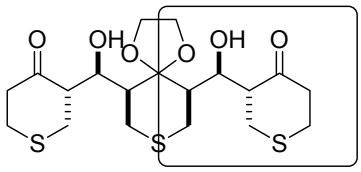
sa

120c



aa

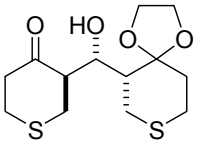
120d



202as

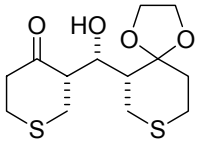
aldol	δ ^{13}C C-5	C-4	C-3	C-2	C-1'
120aa	44.10	209.66	54.59	33.13	72.82
120sa	44.05	209.06	55.33	29.34	69.75
120as	44.64	211.83	55.69	34.58	69.47
120ss	44.45	210.41	56.22	32.85	66.25
202as	44.59	211.64	56.32	33.47	68.64
	Δ δ ^{13}C				
δ202as - δ120aa	0.49	1.98	1.73	0.34	-4.18
δ202as - δ120sa	0.54	2.58	0.99	4.13	-1.11
δ202as - δ120as	-0.05	-0.19	0.63	-1.11	-0.83
δ202as - δ120ss	0.14	1.23	0.10	0.62	2.39

Appendix G: ^{13}C NMR chemical shift difference of 244 with 120a-d.



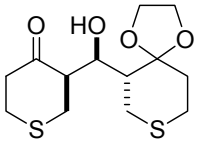
as

120a



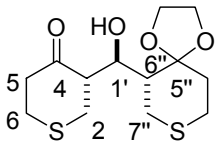
ss

120b



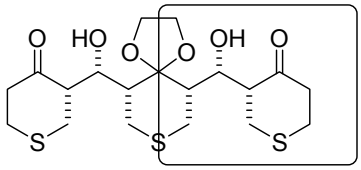
sa

120c



aa

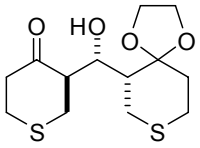
120d



244

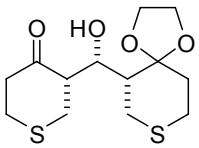
	δ ^{13}C					
	C-5	C-4	C-3	C-2	C-1'	C-7"
120aa	44.10	209.66	54.59	33.13	72.82	29.96
120sa	44.05	209.06	55.33	29.34	69.75	29.70
120as	44.64	211.83	55.69	34.58	69.47	27.57
120ss	44.45	210.41	56.22	32.85	66.25	26.64
244	44.40	209.3	57.62	32.46	66.74	27.01
	Δ δ ^{13}C					
δ244 - δ120aa	0.3	-0.36	3.03	-0.67	-6.08	-2.95
δ244 - δ120sa	0.35	0.24	2.29	3.12	-3.01	-2.69
δ244 - δ120as	-0.24	-2.53	1.93	-2.12	-2.73	-0.56
δ244 - δ120ss	-0.05	-1.11	1.4	-0.39	0.49	0.37

Appendix H: ^{13}C NMR chemical shift difference of 234 with 120a-d.



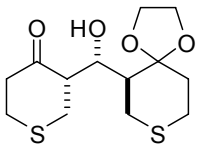
as

120a



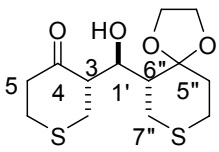
ss

120b



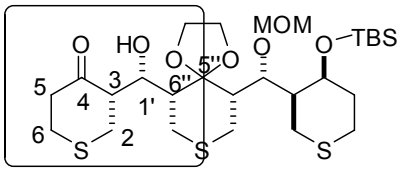
sa

120c



aa

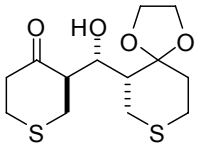
120d



234

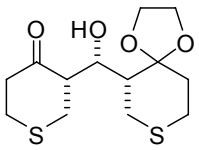
	δ ^{13}C					
	C-5	C-4	C-3	C-1'	C-6"	C-5"
120aa	44.10	209.66	54.59	72.82	46.30	110.42
120sa	44.05	209.06	55.33	69.75	46.24	110.83
120as	44.64	211.83	55.69	69.47	47.18	109.6
120ss	44.45	210.41	56.22	66.25	46.42	110.04
234	44.27	210.13	56.98	66.62	51.49	113.46
	Δ δ ^{13}C					
δ234 - δ120aa	0.17	0.47	2.39	-6.20	5.19	3.04
δ 234 -δ120sa	0.22	1.07	1.65	-3.13	5.25	2.63
δ 234- δ120as	-0.37	-1.70	1.29	-2.85	4.31	3.86
δ 234- δ120ss	-0.18	-0.28	0.76	0.37	5.07	3.42

Appendix I: ^{13}C NMR chemical shift difference of 233 with 120a-d.



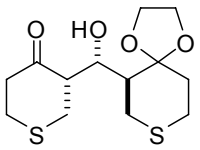
as

120a



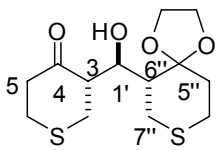
ss

120b



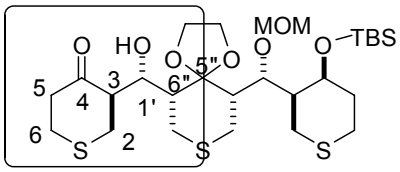
sa

120c



aa

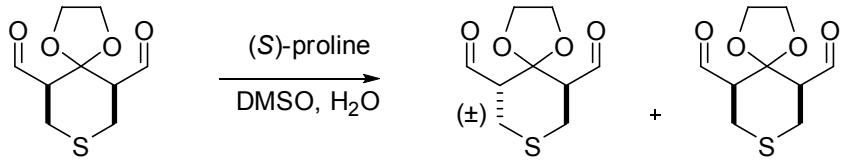
120d



233

	δ ^{13}C					
	C-5	C-4	C-3	C-1'	C-6''	C-5''
120aa	44.1	209.66	54.59	72.82	46.30	110.42
120sa	44.05	209.06	55.33	69.75	46.24	110.83
120as	44.64	211.83	55.69	69.47	47.18	109.60
120ss	44.45	210.41	56.22	66.25	46.42	110.04
233	44.93	212.38	56.61	68.60	51.46	112.51
	Δ δ ^{13}C					
δ233 -δ120aa	0.83	2.72	2.02	-4.22	5.16	2.09
δ233 - δ120sa	0.88	3.32	1.28	-1.15	5.22	1.68
δ233 - δ120as	0.29	0.55	0.92	-0.87	4.28	2.91
δ233 - δ120ss	0.48	1.97	0.39	2.35	5.04	2.47

Appendix J: Determination of isomerization rate constant for 196



196 **223**

ca 3.3:1 equilibrium

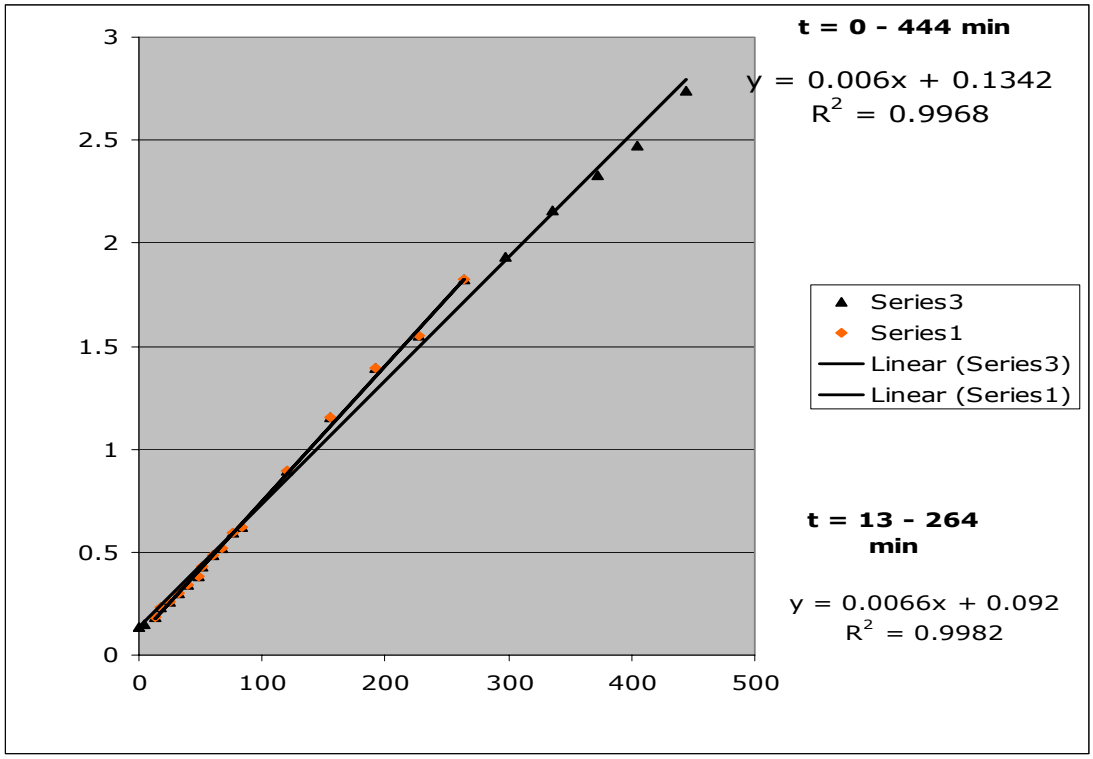
Rt = cis:trans @ time t

Re = cis:trans @ equilibrium

time/mins	Trans	cis	-ln((Rt-Re)÷(Rt+1))
0	1	9.3	0.134919318
5	1	8.3	0.150572858
13	1	6.6	0.187598614
17	1	5.3	0.231111721
25	1	4.7	0.258861634
32	1	4	0.301105093
40	1	3.5	0.340926587
48	1	3.1	0.381367557
52	1	2.7	0.432864082
60	1	2.4	0.481838087
68	1	2.2	0.521296924
76	1	1.9	0.594707108
84	1	1.8	0.624154309
120	1	1.2	0.893817876
156	1	0.9	1.15267951
192	1	0.73	1.392091479
228	1	0.65	1.550597412
264	1	0.55	1.824549292
297	1	0.52	1.932838067
336	1	0.47	2.157219243
372	1	0.44	2.33075597
404	1	0.42	2.470920408
444	1	0.39	2.737249356
1809	1	0.3	= **Re**

Equilibrium is around 3.3:1 trans:cis

$(k_1 + k_2)$ =	$t_{1/2}$ =
0.006	115.5245
0.0066	105.0223



The isomerization proceeds via the formation of an enol and is assumed to be first order at a fixed concentration of proline.

The equilibrium rate constant (k_{obs}) is obtained from the slope of a line drawn from a plot of –ln[(Rt-Re)÷(Rt+1)] versus *t* making use of data points obtained within the the first two half-lives (R_2 > 0.99) where Rt is [**196**]/[**223**] at time *t* and Re is the equilibrium ratio.